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(54) Title: SUBSTITUTED ARYL UREAS AS HIGH POTENCY SWEETENERS

(57) Abstract

Substituted ureas and thioureas are disclosed for use as high potency sweeteners.

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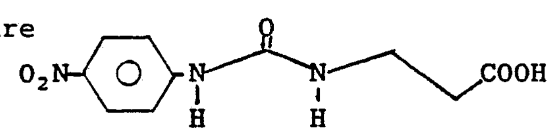
SUBSTITUTED ARYL UREAS AS HIGH POTENCY SWEETENERS

BACKGROUND OF THE INVENTION

This application is a continuation in part of U.S. Serial No. 07/235,396, which is incorporated herein by reference. The present invention relates to substituted aryl ureas and thioureas which are useful as sweetening agents. Additionally, the present invention relates to methods of preparing the novel compounds, as well as sweetening compositions and food products containing ureas and thioureas as sweeteners.

Certain urea and thiourea derivatives are known in the art as sweeteners. The commonly known sweetener, suosan, for example, has the structure



Suosan was reported by Petersen and Muller (Chem. Ber. 1948, 81, 31 and Angew, Chem. 1948, 60A, 58). Other examples of urea and thiourea compounds are found in Z. Lebensm Unters. Forsch. 1982, 175, 266; Japanese Patent 61-260052; Rec. Trav. Chim. 1883, 2, 121; Rec. Trav. Chim. 1884, 3, 223; and J. American Chemical Society 1926, 48, 1069; Naturwissenaschaften 1980, 67, 193; and Naturwissenschaften 1981, 68, 143; and U.S. Patent No. 4,645,678 to Nofre et al.

SUMMARY OF THE INVENTION

In accordance with the present invention, substituted ureas are useful as sweetening agents. (For purposes of this

application, the term "urea" includes inventive compounds which are ureas and thioureas.) The present ureas may be added to food products in amounts sufficient to sweeten food to a desired sweetness level.

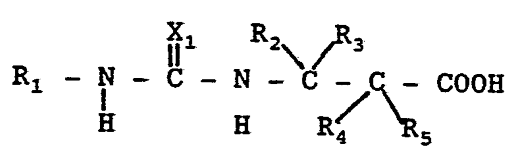
The inventive ureas may be prepared by reacting an isocyanate or isothiocyanate with an amine or aniline. A wide variety of ureas may be manufactured by this method.

Particularly desirable urea compounds include:

N-(4-carbamoylphenyl)-N'-[3-(3-phenylpropionic acid)] urea,
N-(4-cyanophenyl)-N'-[3-(3-phenylpropionic acid)] urea,
N-(4-cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)] urea,
N-(4-ethoxycarbonylphenyl)-N'-[3-(3-phenylpropionic acid)] urea,
N-(4-ethoxycarbonylphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)] urea,
N-(4-nitrophenyl)-N'-[3-(3-phenylpropionic acid)] urea,
N-(4-nitrophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)] urea, and
N-(4-formylphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)] urea.
N-(4-carbamoylphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea.
N-[5-(2-cyanopyridyl)]-N'-[3-(3-phenylpropionic acid)]urea
N-[5-(2-cyanopyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea
N-[5-(2-carbamoylpyridyl)]-N'-[3-(3-phenylpropionic acid)]urea
N-[5-(2-carbamoylpyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea
N-[5-(2-formylpyridyl)]-N'-[3-(3-phenylpropionic acid)]urea
N-[5-(2-formylpyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea

<u>Detailed Description of the Preferred Embodiment</u>

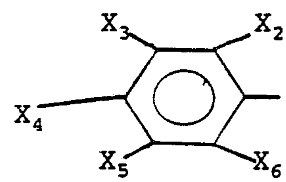
The present substituted ureas are represented by the following formula:



(I)

wherein X_1 is S or O, wherein R_1 is an aryl group including optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic,

optionally substituted bicyclic including optionally substituted bicyclic, or optionally substituted phenyl, where the phenyl corresponds to:



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are selected from the group consisting of:

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
$CH{=}NOCH_3$,
$CH{=}NOH$,
CHO,
CH_2OCH_3,
CH_2OH,
CN,
$COCF_3$,
COC_1-C_3 alkyl,
$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,
$COOC_1$-C_3 alkyl,
COOH,
NH_2,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
Br,
Cl, with the proviso that X_3 and X_5 are not both Cl,
F,
I,
NHCHO,
$NHCOCH_3$,

$NHCONH_2$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 is not OCH_2CH_3
$OCOCH_3$,
OH,
SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2N(C_1$-C_3 alkyl$)_2$,
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring,

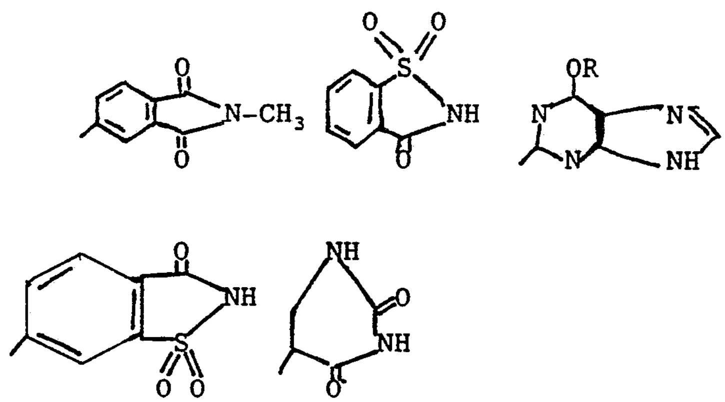
wherein R_2, R_3, R_4, and R_5 are the same or different and are selected from the group consisting of

H,
optionally substituted straight chain or branched C_1-C_{10} alkyl
optionally substituted cyclic C_3-C_{10} alkyl, optionally substituted cyclic,
optionally substituted heterocyclic including optionally substituted heteroaromatics, optionally substituted bicyclic including optionally substituted bicyclic aromatics, or optionally substituted phenyl, and

enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining groups is not H.

Suitable heterocyclic moieties for R_1, R_2, R_3, R_4, or R_5 include optionally substituted pyridines, thiazoles, indoles, naphthyridines, cinnolines, pteridines, thiophenes,

benzothiophenes, naphthothiophenes, thianthrenes, furans, pyrans, isobenzofurans, chromenes, xanthenes, phenoxanthins, pyrroles, isoindoles, indolizines, pyridazines, pyrimidines, pyrazines, pyrazoles, imidazoles, pyrroles, indazoles, purines, quinolizines, isoquinolines, quinolines, phthalazines, quinoxalines, quinazolines, carbazoles, carbolines, phenanthridines, acridines, pyrimidines, phenanthrolines, phenazines, phenarsazines, isothiazoles, phenothiazines, isoxazoles, tetrazoles, triazoles, furazans and heterocyclics of the following formulas:



wherein R is H or C_1-C_6 alkyl. The heterocyclic moieties may be optionally substituted with one or more substituents, such as, for example, C_1-C_6 alkyl, halogen, NO_2, CN, trihalomethyl, carbamoyl, formyl, dihalomethyl, hydroxyl or hydroxyalkyl.

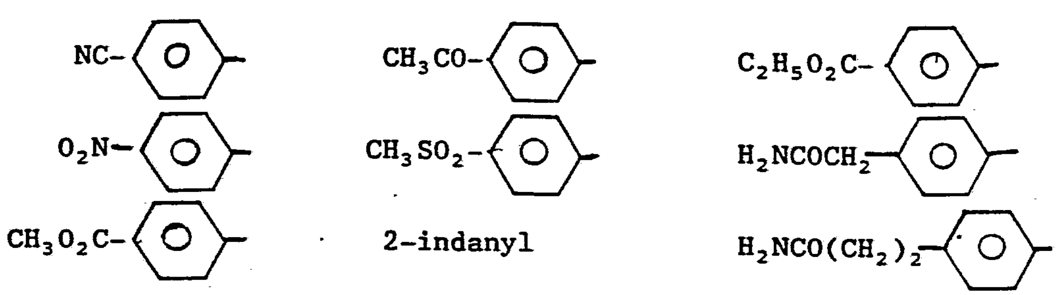
Preferred R_2, R_3, R_4, or R_5 substituents include
H,
pyridyl and substituted pyridyl
phenyl and substituted phenyl
normal alk(en)(yn)yl C_2-C_{13},
branched alk(en)(yn)yl C_3-C_{13},
alk(en)yl cycloalk(en)yl C_4-C_{13},
cycloalk(en)yl alk(en)yl C_4-C_{13},
alk(en)yl cycloalk(en)yl alk(en)yl C_5-C_{13}
alk(en)yl bicycloalk(en)yl C_7-C_{13},
fused bicycloalk(en)yl C_7-C_{13},

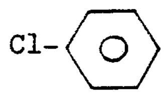
alk(en)yl fused bicycloalk(en)yl C_8-C_{13},
fused bicycloalk(en)yl alk(en)yl C_8-C_{13},
alkenyl fused bicycloalk(en)yl alk(en)yl C_9-C_{13},
fused tricycloalk(en)yl C_{10}-C_{13},
alk(en)yl fused tricycloalk(en)yl C_{11}-C_{13},
fused tricycloalk(en)yl alk(en)yl C_{11}-C_{13}, or
alk(en)yl fused tricycloalk(en)yl alk(en)yl C_{11}-C_{13}.

Specifically preferred R_2, R_3, R_4, or R_5 substituents include $CH(CH_3)C_6H_5$, alkyl substituted S-phenylethyl, diphenylmethyl, pyridyl, pyridyl methyl, piperidyl, homopiperidyl, indolyl, indolinyl, isoindolinyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidyl, indazolyl, quinoxalinyl, quinazolinyl, purinyl, $OCH_2C_6H_5$, pyranyl, tetrahydropyranyl, benzofuranyl, methoxyphenyl, methyloxycarbonylphenyl, 3,4-methylenedioxyphenyl, morpholinyl, benzoxazolyl, acetamidophenyl, cyano, nitro, thienyl, thienyl methyl, tetrahydro-3-thiophene, benzothienyl, 2,2,4,4-tetramethylthiacyclobut-3-yl, thiazolyl, isothiazolyl, $SO_2C_6H_5$, alkyl substituted $-SO_2C_6H_5$ ($SO_2C_6H_2$(2,4,6-trimethyl), $SO_2C_6H_2$(2,4,6-triisopropyl)), SO_2c-C_6H_{11}, SO_2c-C_7H_{13}, 6-oxo-cis-hydrindanyl, chlorophenyl, fluorophenyl, and trifluoromethylphenyl.

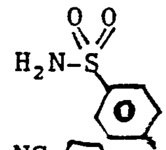
Particularly preferred are those ureas wherein R_2 is selected from the group consisting of pyridyl and substituted pyridyl, benzyl, phenyl and substituted phenyl, benzhydryl, substituted cycloalkyl.

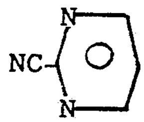
Preferably, the inventive urea is one where R_1 is

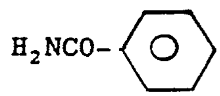


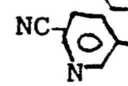


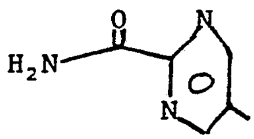
6-indazolyl

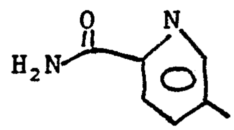












R_2 is phenyl, 3-pyridyl, 2-pyridyl, 4-pyridyl, 4-methoxyphenyl, naphthyl, quinolyl, isoquinolyl or $(CH_2)_{1-6}$(cycloalkyl),

R_3, R_4, and R_5 are H and

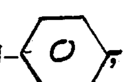
X_1 is O.

There are two isomeric forms (R) and (S) of some preferred compound. The form having more sweetening potency is believed to be the (S) isomer, and is preferred for purposes of this invention.

Particularly preferred compounds include those wherein

R_1 is NC-, $R_2$is 3-pyridyl, R_3, R_4, and R_5 are H, and X_1 is O,

R_1 is NC-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is O_2N-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O,

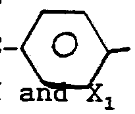
R_1 is $C_2H_5O_2C$-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is $C_2H_5O_2C$-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is H_2NCO-; R_2 is phenyl, R_3, R_4, and R_5 and H and X_1 is O

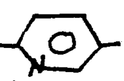
and R_1 is O_2N-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is CHO-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1, is O,

R_1 is $H_2N\overset{O}{\overset{\|}{C}}$-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is NC-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O,

R_1 is NC-, R_2 is 3-pyridyl, R_3, R_4 and R_5 are H and X_1 is O

R_1 is H_2N- $\overset{O}{\overset{\|}{C}}$-, R_2 is phenyl, R_3, R_4 and R_5 are H and X_1 is O

R_1 is H_2N- $\overset{O}{\overset{\|}{C}}$-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O

R_1 is H_2N- $\overset{O}{\overset{\|}{C}}$-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O

R_1 is H_2N- $\overset{O}{\overset{\|}{C}}$-; R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O

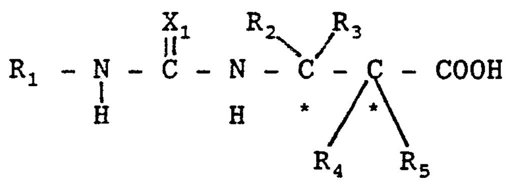
R_1 is OHC-, R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O

R_1 is OHC-, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O

R_1 is OHC-; R_2 is phenyl, R_3, R_4, and R_5 are H and X_1 is O

R_1 is OHC, R_2 is 3-pyridyl, R_3, R_4, and R_5 are H and X_1 is O.

The present ureas also include physiologically acceptable salts of the compounds described above. The ureas also may have two asymmetrical carbon atoms, i.e., optically active sites as asterisked in the following structure:



These ureas exist in (R) and (S) enantiomeric forms if there is one optically active site. If both sites are optically active, there are four possible diastereomic forms: (R)(R), (R)(S), (S)(R), and (S)(S).

The present invention also relates to edible products containing the present urea compounds as sweetening agents either alone or in combination with other sweeteners. Also provided by the present invention is a process for sweetening edible products such as foods, beverages, chewing gums, confections, pharmaceuticals, veterinary preparations and the like.

The present invention further contemplates compositions of the present ureas in combination with other sweetening agents and/or physiologically acceptable carriers which may be bulking agents. Suitable carriers include water, polymeric dextrose such as polydextrose, starch and modified starches, maltodextrins, cellulose, methylcellulose, maltitol, cellobiitol, carboxymethylcellulose, hydroxypropylcellulose, hemicelluloses microcrystalline cellulose, other cellulose derivatives, sodium alginate, pectins and other gums, lactose, maltose, glucose, leucine, glycerol, mannitol, sorbitol, sodium bicarbonate and phosphoric, citric, tartaric, fumaric, benzoic, sorbic, propionic acids and their sodium, potassium and calcium salts and mixtures

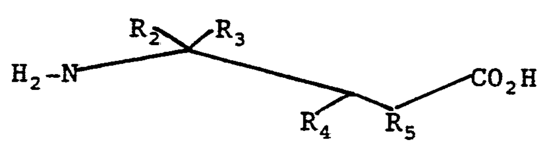
of all of the above.

Suitable sweetening agents which may be used in combination with the present ureas can be sugars or high potency sweeteners such as sucrose, corn syrups, fructose, high fructose corn syrup, aspartame, alitame, neohesperidin dihydrochalcone, hydrogenated isomaltulose (Palatinite), stevioside type sweeteners, L-sugars, glycyrrhizin, xylitol, lactitol, neosugar, acesulfam-K, saccharin (sodium, potassium or calcium salt), cyclamic acid (sodium, potassium or calcium salt), sucralose, monellin and thaumatin and mixtures thereof.

The present invention also relates to a novel method of preparing the inventive urea compounds. An isocyanate of the formula

$$R_1NCX_1$$

with R_1 and X_1 chosen as desired from the substituents earlier disclosed is reacted with a substituted beta-amino acid, such as a beta-alanine of the formula



with R_2, R_3, R_4, and R_5 chosen as desired from the substituents earlier disclosed. The ester of the β amino acids may also be used. The substituted beta-amino acid may be prepared by the methods disclosed in:

U.S. Patent 4,127,570 to Fosker
Journal of the Chemical Society (1936), V.59, p.299
Journal of the Chemical Society (1929), V.51, P.41
Liebigs Ann. Chemistry (1981), V.12, p.2258
Synthetic Communication (1981), V.11, p.95
Synthesis (1982), p. 967
Chem. Pharm. Bull. (1978), <u>26</u>, 260-263
each of which is incorporated herein by reference.

The isocyanate and substituted beta-amino acid may be reacted in the presence or absence of a base. The reaction is preferably carried out in the presence of a solvent such as acetonitrile, a mixture of acetonitrile and water, methanol, acetone, or a mixture of ethyl acetate and water.

Anilines may also be reacted with isocyanates or isothiocyanates of a substituted β-amino acid ester followed by ester hydrolysis.

In some of the desired compounds, it is preferable to isolate one of two enantiomeric forms. An aldehyde and a chiral amine are reacted to produce a Schiff base. The Schiff base is reacted with a methyl haloacetate in THF with a metal such as zinc to produce a diastereomeric mixture of a β-lactam. The desired diastereomer is separated after the β-lactam is hydrolyzed and esterified to produce an ester of a first β-amino acid. After hydrogenolysis, the desired stereoisomer of a second β-amino acid is obtained.

For some applications, esterification is not necessary. In these applications, the desired diastereomer of the β-lactam is isolated and then hydrolyzed to produce a diastereomeric mixture of a first β-amino acid. The first β-amino acid is then hydrogenolyzed to produce the desired stereoisomer of a second β-amino acid.

The present invention also relates to a method of sweetening foods or comestible products. In such uses, the present ureas are added to any consumable product in which it is desired to have a sweet taste. The inventive urea compounds are added to such products in amounts effective to impact the desired level of sweetness. The optimum amount of the urea sweetener agent will vary depending on a variety of factors, including the sweetness potency of a particular urea sweetening agent, storage and use conditions of the product, the particular components of the product, the flavor profile of the comestible product, and the level of sweetness desired. One skilled in the art can readily determine the optimum amount of sweetening agent to be employed

in a particular formulation of a food product by conducting routine sweetness (sensory) experiments. Usually, the present sweetening agents are added to the comestible products in amounts of from about 0.00001 to about 0.1 percent by weight of the comestible product, advantageously from about 0.00005 to about 0.05 weight percent and preferably from about 0.001 to about 0.02 weight percent. Concentrates, of course, will contain higher percentages of sweetening agent(s), and are diluted for end use purposes.

Suitable products which are sweetened by the present sweetening agents include any products for which a sweet flavor component is desired such as food products (for human or animal consumption), beverages (alcoholic, soft drinks, juices, carbonated beverages), confectionary products (candies, chewing gum, baked goods, pastries, breads, etc.), hygiene products, cosmetics, pharmaceutical products and veterinary products. In sweetening gum, the present ureas can be added in amounts in excess of a sucrose equivalent normally found in gum. This excess amount of urea sweetener may provide a longer sweet taste due to its lower solubility compared to sucrose and enhancement of flavor (flavor enhancer).

The present ureas can be added in pure form to foods to impart a sweet flavor. However, because of the high sweetness potency of the present sweetening agents, they are typically admixed with a carrier or bulking agent. Suitable carriers or bulking agents include water, polymeric dextrose such as Polydextrose, starch and modified starches, maltodextrins, cellulose, hemicellulose, methylcellulose, carboxymethylcellulose, cellobiitol, hydroxypropylcellulose, hemicelluloses microcrystalline cellulose, cellulose derivatives, sodium alginate, pectins and other gums, lactose, maltose, maltitol, glucose, leucine, glycerol, mannitol, sorbitol, sodium bicarbonate and phosphoric, citric, tartaric, fumaric, benzoic, sorbic and propionic acids and their sodium, potassium and calcium salts and mixtures of all of the above.

The present ureas can be employed alone as the sole

sweetening agent in a comestible product. Mixtures of more than one of the inventive ureas can also be employed. Additionally, the ureas can be used in combination with other sweetening agents such as sugars (such as fructose and sucrose), corn syrups, high potency sweeteners such as aspartame and alitame, and other sweeteners such as glycyrrhizin, aminoacyl sugars, xylitol, sorbitol, mannitol, acesulfam K, thaumatin, monellin, cyclamates, saccharin, neohesperidin dihydrochalcone, hydrogenated isomaltulose, (Palatinit), stevioside type sweeteners, lactitol, neosugar, L-sugars, sucralose, and mixtures thereof.

The compounds synthesized were tasted as aqueous solutions at 1 mg/ml and 10 fold dilutions thereof and compared in taste quality and intensity to a sucrose standard solution. All compounds were found to be sweet.

The following examples illustrate the practice of the present invention, but should not be construed as limiting its scope.

EXAMPLES

EXAMPLE 1

Preparation of N-(4-Ethoxycarbonylphenyl)-N'-[3-(3-phenylpropionic acid)]urea.

To a stirred solution of 4-ethoxycarbonylphenyl isocyanate (2.16 g, 11.3 mmol) in 35 ml of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.90 g, 11.5 mmol) and sodium hydroxide (0.458 g, 11.5 mmol) in a mixture of 6 ml of water and 6 mL of acetonitrile. The reaction mixture was stirred for 16 hours, then concentrated. The residue was diluted with water (50 ml) and extracted with methylene chloride (25 mL) and ethyl acetate (25 ml). The aqueous layer was acidified with 11.5 mL of 1 N HCl and stirred for 30 minutes. The resulting slurry was filtered and the solid was washed with copious amounts of water. The solid was dried *in vacuo* to afford 3.61 g (90%) of the urea as white powder. PMR (dmso-D_6) δ 12.3 (s, 1 H), 9.03 (s, 1 H),

7.82, 7.50 (abq, 4H), 7.45-7.2 (m, 5 H), 6.96 (d, 1H, J= 8.4 Hz), 5.14 (overlapping dt, 1H), 4.24 (q, 2 H, J= 7 Hz), 2.78 (m, 2 H), 1.28 (t, 3 H, J= Hz). CMR (dmso-D_6) δ 172.0, 165.5, 153.9, 144.9, 142.6, 130.3, 128.3, 127.0, 126.3, 122.1, 116.7, 60.2, 50.0, 40.9, 14.2 IR(KBr)cm^{-1} 3400, 3340, 3200, 2980, 1710, 1650, 1595, 1553, 1512, 1409. Anal. calcd. for $C_{19}H_{20}N_2O_5$-0.17 H_2O: C, 63.49; H, 5.70; N, 7.79. Found: C, 63.47: H, 5.68: N, 7.63.

EXAMPLE 2

Preparation of N-(4-Acetylphenyl)-N'-[3-(3-phenylpropionic acid)]urea.

To a stirred solution of 4-acetylphenyl isocyanate (1.87 g, 11.6 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.95 g, 11.8 mmol) and sodium hydroxide (0.472 g, 11.8 mmol) in a mixture of 6 ml of water and 6 ml of acetonitrile. Solid formed in the reaction material immediately. The reaction mixture was stirred for 17 hours, then concentrated. The residue was diluted with water (75 ml) and extracted with ethyl acetate (2 x 25 mL ea.) The aqueous layer was concentrated to remove traces of ethyl acetate. The aqueous layer was then acidified with 14 ml of 1 N HCl and the product gummed out. The resulting suspension was stirred and the gum solidified. The slurry was filtered and the solid was washed with copious amounts of water. The solid was dried in vacuo to afford 3.30 g (87%) of the urea as tan powder. The crude product was recrystallized from acetonitrile to afford 1.67 g (44%) of the urea. PMR (dmso-D_6) δ 12.3 (s, 1 H), 9.01 (s, 1 H), 7.81 (d, 2 H, J= 8.8 Hz), 7.47 (d, 2H, J= 8.8 Hz), 7.4-7.15 (m, 5 H), 6.95 (d, 1H, J= 8.4 Hz), 5.11 (apparent q, 1 H), 2.85-2.6 (m, 2 H), 2.45 (s, 3 H). CMR (dmso-D_6) δ 196.2, 172.0, 153.9, 144.9, 142.6, 129.6, 128.3, 127.0, 126.3, 116.7, 49.9, 40.9, 26.3.

EXAMPLE 3

Preparation of N-(4-Bromophenyl)-N'-[3-(3-phenylpropionic acid)]urea.

To a stirred solution of 4-bromophenyl isocyanate (2.69 g, 13.6 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (2.29 g, 13.9 mmol) and sodium hydroxide (0.555 g, 13.9 mmol) in a mixture of 6 ml of water and 6 mL of acetonitrile. The reaction mixture was stirred for 24 hours, then concentrated. The residue was diluted with water (75 ml) and extracted with ethyl acetate (2 x 50 ml). The aqueous layer was concentrated to remove traces of ethyl acetate and then acidified with 20 mL of 1 N HCl. The resulting thick slurry was diluted with water and filtered. The solid was washed with copious amounts of water and dried in vacuo to afford 3.61 g (90%) of the urea as white powder. PMR (dmso-D_6) δ 12.3 (bs, 1 H), 8.73 (s, 1 H), 7.45-7.2 (m, 9H), 6.84 (d, 1H, J= 8.4 Hz), 5.11 (apparent q, 1 H), 2.85-2.65 (m, 2 H). CMR (dmso-D_6) δ 172.0, 154.1, 142.7, 139.7, 131.4, 128.3, 126.9, 126.3, 119.5, 112.4, 49.9, 40.9.

EXAMPLE 4

Preparation of N-(4-cyanophenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 1.652 g (11.5 mmol) of 4-cyanophenyl isocyanate in 50 mL acetonitrile was added 1.893 g (11.5 mmol) of 3-amino-3-phenylpropionic acid slurried in 50 ml acetonitrile. After 1 hour at room temperature the reaction mixture was heated to reflux where, after the addition of an additional 50 ml of acetonitrile, a clear solution formed. The reaction mixture was cooled with stirring overnight. The solids were filtered off and dried at 40° C/1 mm Hg to a constant weight of 3.01 g (84.6%) of the desired urea, m.p. 190-192° C IR (KBr) 3380, 3320, 2230,

1680, 1600, 1540, 1320, 1240 cm^{-1}. ^{1}H NMR (Me_2SO-d_6, 300MHZ) δ 2.6-2.7 (d,2H), 4.9-5.1 (m,1H), 6.9 (d,1H), 7.0-7.6 (m, 9H), 9.0 (s,1H); ^{13}C NMR (Me_2SO-d_6, 75.5MHZ) δ 172.8, 154.6, 145.6, 143.3, 134.0, 127.8, 127.1, 120.2, 118.3, 103.4, 50.8, 41.6. Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.15; H, 4.92; N, 13.92.

EXAMPLE 5

Preparation of N-(4-Cyanophenyl)-N′-[3-(3-(3-pyridyl)propionic acid)]urea Sodium salt

To a solution of 1.66 g (10 mmol) of 3-amino-3-(3-pyridyl) propionic acid, 0.4 g of NaOH, and 50 ml H_2O was added 2.88 g (20 mmol) of 4-cyanophenyl isocyanate in 50 ml ethyl acetate. The reaction mixture was stirred overnight at room temperature. The two phase mixture was filtered to remove traces of impurities and the aqueous phase was twice extracted with ethyl acetate. The water was removed at reduced pressure to produce a gummy mass. TLC and ^{1}H NMR indicated the material to be a mixture of desired urea and starting beta-amino acid. The desired urea was isolated by reverse phase chromatography using acetonitile/water as the mobile phase. IR (KBr) 3400, 2230, 1700, 1600, 1560, 1400 cm^{-1}. $_1$H NMR (Me_2SO-d_6, 300MHz) δ 2.5 (d,2H), 5.1 (s,1H), 7.3 (m,1H), 7.5 (d,2H), 7.6 (d,2H), 7.65 (s,1H), 8.35 (d,1H), 8.55 (s,1H), 9.3 (d,1H); ^{13}C NMR (Me_2SO-d_6, 75.5 MHz) δ 174.8, 154.7, 147.8, 147.0, 146.1, 140.7, 133.5, 132.6, 123.0, 119.6, 117.2, 101.0, 49.7, 45.0.

EXAMPLE 6

Preparation of N-(4-Nitrophenyl)-N′-[3-(3-phenylpropionic acid)]urea

To a slurry of 1.652 g (10 mmol) of 3-amino-3-phenylpropionic acid in 50 ml acetone was added 1.641 g (10 mmol) of

4-nitrophenyl isocyanate dissolved in 5 ml acetone. After 4 hours of stirring at room temperature, a trace of insoluble impurities was removed by filtration. After removal of the solvent a bright yellow solid was isolated in a quantitative yield. The crude product was purified on a silica column using a chloroform:methanol:acetic acid solvent. IR (KBr) 3400, 1700, 1560, 1500, 1350 cm^{-1}. ^1H NMR (Me_2SO-d_6, 300MHz) δ 2.75 (bs,2H), 5.2 (d,1H), 7.2-7.4 (m,5H), 7.65 (d,2H), 7.85 (m,1H), 8.1 (d,2H), 10.1 (s,1H); ^{13}C NMR (Me_2SO-d_6, 75.5 MHz) δ 153.9, 147.4, 143.3, 140.2, 128.1, 126.6, 126.3, 124.9, 116.7, 50.5. Anal. Calcd for $C_{16}H_{15}N_3O_5(2H_2O)$: C, 52.59; H, 5.24: N, 11.50. Found: C, 52.14; H, 4.70; N, 11.56.

EXAMPLE 7

Preparation of N-4-Carbamoylphenyl-N'-(3-(3-phenylpropionicacid) urea

Methyl 3-isocyanato-3-phenylpropionate was first prepared.

The reaction assembly is as follows: a 100 mL three-neck round bottom flask was fitted with a thermometer, reflux condenser, and gas inlet bubble tube. The condenser was connected to a trap and then to an aqueous NaOH bath (phosgene scrubber). The gas inlet line consisted of a T-tube with nitrogen and phosgene inlets at two of the openings. The exit led through a trap and into the gas bubble tube.

The apparatus was purged with nitrogen, toluene (20 mL) was added and the solution chilled in an ice-salt bath to 0 °C. Gaseous phosgene (10 mL, 14 g, 140 mmol; actual measurement based on volume increase of the toluene solution) was added and a slow addition of phosgene was continued throughout the remainder of the reaction. Methyl 3-phenyl-3-aminopropionate was added portionwise over 2 min. to the phosgene solution. The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to room temperature over 30 min, and then carefully heated and held at

110 °C for 4 hours (slow phosgene addition was continued). The resulting clear solution was allowed to cool to room temperature, purged with nitrogen overnight and then concentrated (asp vacuum) yielding an oil. Vacuum distillation using a Kugelrohr apparatus (70 °C, 1 mm) afforded the pure isocyanate (8.95 g, 94 %): ^1H NMR ($CDCl_3$) δ 7.42 (m, 5 H), 5.12 (q, J = 4.7 Hz, 1 H), 3.71 (s, 3 H), 2.79 (m, 2 H); IR (thin film) cm^{-1} 2251, 1745, 1438, 1269, 1199, 1170, 987, 760, 700. Anal. Calcd for $C_{11}H_{11}N_1O_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.52; H, 5.55; N, 6.81.

N-(4-Carbamoylphenyl)-N'-[(3-(methyl 3-phenylpropionate)] was then prepared by the following procedure.

To a solution of methyl 3-isocyanato-3-phenylpropionate (1.97 g, 9.59 mmol) in CH_3CN (35 mL) was added 4-aminobenzamide (1.31 g, 9.59 mmol) with stirring at room temperature. The resulting clear solution was allowed to stand for 3 weeks during which time a white precipitate formed. Vacuum filtration yielded the desired urea (3.06 g, 94 %) as a white solid; mp 198-200 °C; ^1H NMR ($DMSOd_6$) δ 8.78 (s, 1 H), 7.71 (d, J = 9.3 Hz, 2 H), 7.37 (d, J = 9.3 Hz, 2 H), 7.36-7.18 (m, 5 H), 7.10 (s, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 5.12 (q, J = 7.8 Hz, 1 H), 3.54 (s, 3 H), 2.82 (m, 2 H); IR (KBr) cm^{-1} 3354, 1730, 1669, 1659, 1528, 701. Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.29; H, 5.82; N, 12.43.

LiOH (0.31 g, 7.3 mmol) in H_2O (5 mL) was added via syringe pump over 4 hr to a solution of N-(4-carbamoylphenyl)-N'-[3-(methyl 3-phenylpropionate)] (2.50 g, 7.32 mmol) in CH_3OH/H_2O (2:1, 75 mL). The resulting suspension was stirred for 36 hr and filtered. The aqueous filtrate was washed with methylene chloride (3 X 25 mL) and then acidified to pH 3 with 1 N HCl, yielding the desired acid, N-(4-carbamoylphenyl)-N'-[3-(3-phenylpropionic acid)]urea (1.75 g, 73 %) as a white solid: mp 201-212 °C with decomp; ^1H NMR (CD_3OD) δ 8.82 (s, 1 H), 7.76 (s) and 7.71 (d, J = 8.6), (3 H),

7.37 (d, J = 8.6 Hz, 2 H), 7.34-7.17 (m, 5 H), 7.09 (s, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 5.13-5.05 (m, 1 H), 2.73 (d, J = 7.0 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.5, 168.0, 154.5, 143.6, 143.1, 129.0, 128.8, 127.4, 127.1, 126.8, 116.9, 50.4, 41.4. IR (KBr) 3343, 1693, 1661, 1649, 1604, 1543, 1414, 1239, 852, 762, 699. Anal. Calcd for $C_{17}H_{17}N_3O_4(0.84\ H_2O)$: C, 59.62; H, 5.50; N, 12.27. Found: C, 59.62; H, 5.26; N, 12.18.

EXAMPLE 8

Preparation of N-(4-Sulfonamidophenyl)-N'-[3-(3-phenylpropionic acid)]urea

Methyl 3-isocyanato-3-phenylpropionate was prepared by the procedure of Example 7. To a solution of methyl 3-isocyanato-3-phenylpropionate (1.59 g, 7.75 mmol) in acetonitrile (50 mL) was added sulfanilamide (1.33 g, 7.75 mmol) in one portion with stirring. The resulting homogenous solution was allowed to stand for 3 weeks, during which time a white precipitate formed. Vacuum filtration yielded N-4-sulfonamidophenyl)-N'-[3-(methyl 3-phenylpropionate)]urea as a white solid (2.35 g, 80.5 %). mp 221-222 °C; ^1H NMR (DMSO) δ 8.93 (s, 1 H), 7.63 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.38-7.18 (m, 5 H), 7.13 (s, 2 H), 6.93 (d, J = 8.4 Hz, 1 H), 5.11 (q, J = 7.5 Hz, 1 H), 3.52 (s, 3 H), 2.93-2.76 (m, 2 H). IR (KBr)Cm^{-1} 3800-2800 (br), 1723, 1688, 1682, 1594, 1392, 1493, 1333, 1239, 1157, 1015, 837, 702, 607. Anal. Calcd for $C_{17}H_{19}N_3O_5S_1$: C, 54.10; H, 5.07; N, 11.13; S, 8.50. Found: C, 54.36; H, 5.22; N, 10.91; S, 8.56.

To a stirred solution of methyl ester from above (2.00 g, 5.30 mmol) in methanol/water (3:2, 50 mL) was added LiOH (0.22 g, 5.30 mmol) in water (5 mL) over 4 hr. The resulting suspension was filtered. The filtrate was washed with methylene chloride (3 X 15 mL), and then acidified (1 N HCl) to pH 2 yielding N-(4-sulfonamidophenyl)-N'-[3-(3-phenylpropionic acid)]urea as a

white solid (1.08 g, 56 %): mp 165-167 °C with decomposition; ^{1}H NMR (DMSO-d_6) δ 8.96 (s, 1 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.47 (d, J = 8.8 Hz, 2 H), 7.39-7.18 (m, 5 H), 7.13 (s, 2 H), 6.93 (d, J = 8.3, 1 H), 5.08 (q, J = 7.8 Hz, 1 H), 2.73 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 40.87, 49.97, 116.83, 126.31, 126.75, 127.00, 128.32, 136.14, 142.54, 143.41, 154.00, 172.04; IR (KBr) cm^{-1} 3650-2800 (br), 1883, 1840, 1592, 1541, 1326, 1155. Anal. Calcd for $C_{16}H_{17}N_3O_5S_1(1\ H_2O)$: C, 50.39; H, 5.02; N, 11.02; S, 8.41. Found: C, 50.75; H, 4.96; N, 10.90; S, 8.31.

EXAMPLE 9

Preparation of N-(4-Carbomethoxyphenyl)-N'-[3-(3-phenylpropionic acid)]urea

A solution of 3-amino-3-phenylpropionic acid (3.19 g, 19.3 mmol) and NaOH (0.77 g, 19.3 mmol) in water/acetonitrile (1:1, 20 mL) was added in three portions over 15 min to a vigorously stirred solution of 4-methoxycarbonylphenyl isocyanate (3.00 g, 19.3 mmol) in acetonitrile (20 mL). The acetonitrile was removed by rotary evaporation and the resulting aqueous solution was washed with ethyl acetate (2 X 25 mL). After acidification of the aqueous phase (pH 2) with 1 N HCl, the desired urea precipitated (3.61 g, 55 %) as a white solid: mp 111-112 °C with decomposition; ^{1}H NMR (DMSO-d_6) δ 9.01 (s, 1 H), 7.79 (d, J = 8.7 Hz, 2 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.40-7.17 (m, 5 H), 6.95 (d, J = 8.4 Hz, 1 H), 5.10 (q, J = 7.2 Hz, 1 H), 3.76 (s, 3 H), 2.75 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.48, 166.41, 154.39, 145.40, 142.99, 130.79, 128.74, 127.41, 126.76, 122.28, 117.16, 52.08. 50.41, 41.31; IR (KBr) cm^{-1} 3600-2400 (br), 1712, 1657, 1594, 1548, 1436, 1411, 1285, 1245, 1176, 1113, 765, 700. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.09; H, 5.45; N, 7.89.

EXAMPLE 10

Preparation of
N-4-(Carboethoxyphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea

To a solution of $NaHCO_3$ (2.13 g, 25.3 mmol) in water (5 mL) was added 3-amino-3-(3-pyridyl)propionic acid (4.21 g, 25.3 mmol). The resulting solution was concentrated (5 mm vacuum)to dryness and ethanol was added (20 mL). This suspension was concentrated (5 mm vacuum) and the ethanol treatment and concentration was repeated a second time. The white solid thus formed was suspended in methanol (50 mL) and carboethoxyphenyl isocyanate (4.84 g, 25.3 mmol) added in one portion which resulted in the formation of a clear solution. After 4 hr, the solution was concentrated to 15 mL and additional carboethoxyphenyl isocyanate (1.2 g, 6.3 mmol) was added. Concentration of this solution (5 mm vacuum) afforded a white solid. Water (10 mL) was added to the solid and after vigorous stirring, the suspension was filtered. The filtrate was washed with methylene chloride (2 X 5 mL) and concentrated (5 mm vacuum) providing a white foam. This material was purified by reverse phase high pressure liquid chromatography (100 % water) and afforded the desired product as sodium salt (white solid): mp 190-195°C with decomposition; ^1H NMR (DMSO-d_6) δ 10.92 (s, 1 H), 8.91 (d, J = 6.0 Hz, 1 H), 8.65 (s, 1 H), 8.40 (d, J = 4.4 Hz, 1 H), 7.79 (d, J = 8.8 Hz, 3 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.31 (d of d [J = 4.8 and 7.7 Hz, 1 H), 5.19 (q J = 6.4 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 2.60 (m, 2 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 175.66, 165.98, 155.25, 148.51, 147.57, 146.43, 141.05, 134.22, 130.36, 123.51, 121.47, 116.98, 60.35, 50.02, 45.10, 14.55; IR (KBr) cm^{-1} 3700-2600 (br), 1693, 1597, 1547, 1411, 1285, 1176. Anal. Calcd for $C_{18}H_{18}N_3O_5Na_1(1.3\ H_2O)$: C, 53.68; H, 5.16; N, 10.43. Found: C, 53.66; H, 4.85; N, 10.44.

EXAMPLE 11

Preparation
of N-(4-Carbamoylphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea

Procedure A:

A solution of 3-amino-3-(3-pyridyl)propionic acid (4.21 g, 25.3 mmol) in water (10 mL) was treated with NaOH (1.01 g, 25.3 mmol) forming the sodium salt. This solution was added to a solution of 4-carboethoxyphenyl isocyanate (7.62 g, 39.9 mmol) in acetonitrile (60 mL). After stirring for 2 days, less than 5 % of the starting amino acid remained unreacted as determined by HPLC. The resulting suspension was filtered. The remaining acetonitrile was removed by vacuum evaporation and water (20 mL) added to the solution. The resulting aqueous solution was washed with ethyl acetate (3 X 10 mL) and concentrated (5 mm) yielding the crude product as a gummy oil. ^{1}H NMR (DMSO-d_6) δ 10.78 (s, ca. 1 H), 8.73 (d, J = 5.7 Hz, ca. 1 H), 8.58-8.52 (m, 1 H), 8.43-8.32 (m, 1 H), 7.75-7.65 (d, J = 8.6 Hz, 3 H). 7.53 (d, J = 8.6 Hz, 2 H), 7.35-7.20 (m, 1 H), 5.00 (q, J = 6.7 Hz, 1 H), 4.20 (q, J = 7.6 Hz, 2 H), 1.52-2.40 (m, 2 H), 1.24 (t, J = 7.6 Hz, 3 H).

To the above crude product (2.5 g, 7.0 mmol) in a Parr Type high pressure reactor was added NH_4OH (150 mL, 14.8 M) and the solution heated to 80 °C for 4.5 hr. The resulting solution was concentrated yielding a syrup. The syrup was chromatographed on an HPLC system using Whatman Partisil 20, C_{18} packing using 100 % H_2O. When the desired product began to elute, the solvent strength was increased to acetonitrile:water (2.5:97.5). The fractions containing the product were combined and concentrated (5 mm) until only about 25 mL of solution remained. This solution was lyophilized yielding the desired product as a white solid (0.610 g, 25 %), obtained as a mixture of sodium and

ammonium salts: ^1H NMR (DMSO-d_6) δ 9.52 (s, 1 H), 8.53 (s, 1 H), 8.36 (d, J = 5.7 Hz, 1 H), 8.17 (d, J = 5.7 Hz, 1 H), 7.78-7.62 (m, 4 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.29-7.21 (m, 1 H), 7.05 (s, 1 H), 4.97 (q, J = 6.7 Hz, 1 H), 2.43 (m, 2 H); IR (KBr) cm^{-1} 3600-2800 (br), 1663, 1585, 1539, 1412, 1396, 1328, 1316, 1242, 1185, 1115, 851, 769, 711.

Procedure B:

Conversion of N-(4-Cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)] urea to sodium salt of N-4-Carbamoylphenyl-N'-[3-(3-(3-pyridyl)propionic acid)] urea:

Hydrogen peroxide (30%, 3.45 mL, 9.60 mmol) was added to a stirred suspension of N-(4-cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea was prepared as detailed in Example 5 and 2.90 g, 9.60 mmol was placed in ethanol (6.9 mL), water (6.9 mL) and sodium hydroxide (6N, 2.07 mL, 12.42 mmol). The reaction mixture was stirred for 15 min at room temperature until the contents of the flask became clear and the evolution of gas (oxygen) stopped. Sodium bisulfite (2g) was added to the reaction mixture to destroy excess hydrogen peroxide. The reaction mixture was concentrated in vacuo at room temperature and then chromatographed (reverse phase HPLC, water as the eluant). Pure fractions were combined and lyophilized to afford 1.90 g (62%) of the desired product as a white crystalline powder. ^1H NMR (D_2O) δ 2.70 (d, 2H, J=7.3 Hz), 5.10 (t, 1H, J=7.1 Hz), 7.33 and 7.68 (AB quartet 4H, J=7.6 Hz), 7.38-7.43 (m, 1H), 7.84 (d, 1H, J=8.0 Hz), 8.39 (d, 1H, J=4.4 Hz), 8.51 (s, 1H). Anal Calcd for $C_{16}H_{15}N_4NaO_4(1.5H_2O)$: C, 50.93; H, 4.8: N, 14.84. Found: C, 50.83; H, 4.20; N, 14.27

EXAMPLE 12

Preparation of N-(4-Carboxyphenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea

To a stirred solution of the ethyl ester produced in Example 10 (3.00 g, 7.91 mmol) in water was added NaOH (8.7 mL, 8.7 mmol, 1N). After 20 hr, no starting materials remained as determined by HPLC. The reaction mixture was concentrated (5 mm vacuum), dissolved in water (5 mL), filtered (Acrodisc-HPLC filter), and purified by high pressure liquid chromatography (Whatman partisil-20, ODS-3). Concentration (5 mm vacuum) to 50 mL followed by lyophilization afforded the desired diacid as a white solid, as the disodium salt; ^1H NMR (D_2O with 5 % DMSO-d_6) δ 8.40 (s, 1 H), 8.19 (s, 1 H), 7.80-7.55 (m, 3 H), 7.28-7.07 (m, 3 H), 5.15-4.95 (m, 1 H), 2.73-2.48 (m, 2 H); ^{13}C NMR (D_2O with 5 % DMSO-d_6) δ 178.50, 175.05, 156.35, 147.45, 146.82, 141.31, 138.78, 135.18, 130.43, 130.17, 124.33, 118.66, 50.08, 43.97; IR (KBr) cm^{-1} 3700-2400 (br), 1688, 1603, 1387, 1311, 1239, 792, 702. Anal. Calcd for $C_{16}H_{13}N_3O_5Na_2$ (3.51 H_2O): C, 44.01; H, 4.63; N, 9.62. Found: C, 44.02; H, 4.15; N, 9.71.

EXAMPLE 13

Preparation of N-(4-Iodophenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 4-iodophenyl isocyanate (2.45 g, 10.0 mmol) in 30 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.67 g, 10.1 mmol) and sodium hydroxide (0.404 g, 10.1 mmol) in 10 mL of 1:1 acetonitrile-water. Precipitation of a white solid made the reaction suspension difficult to stir, and it was diluted with 10 mL of acetonitrile and 10 mL of water. The milky white solution was stirred at room temperature for 16.5 h, and then the acetonitrile removed at reduced pressure. The aqueous residue was diluted to 150 mL with

water,and then extracted with three portions of ethyl acetate. The aqueous solution was made basic with 1 N sodium hydroxide, then filtered to remove a white solid. The solid was washed with water and then dried in vacuo at 60 °C. This material, 1.74 g (40%) was identified as the sodium salt of the desired product. The filtrate was acidified to pH 1 with conc. hydrochloric acid. The precipitate was filtered, washed with water and ether, then dried in vacuo at 60 °C to give 1.15 g (28%) of a white solid: mp: 208-209 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.70 (s, 1 H), 7.52-7.20 (AB, 4 H, J_{AB}=8.8 Hz), 7.33-7.28 (m, 5 H), 6.83 (d, 1 H, J=8.4 Hz), 5.12-5.08 (m, 1 H), and 2.76-2.73 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.2, 154.3, 142.8, 140.3, 137.3, 128.4, 127.1, 126.4, 120.1, 83.9, 50.0, and 41.1; IR (KBr): 3338, 3304, 3064, 3032, 2928, 1705, 1651, 1592, 1547, 1486, 1398, 1314, 1240, and 712 cm^{-1}. Analysis: Calculated for $C_{16}H_{15}IN_2O_3(H_2O)_{0.37}$: C 46.08; H 3.81; N 6.72. Found: C 46.07; H 3.73; N 6.75.

EXAMPLE 14

Preparation of N-(4-Chlorophenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 4-chlorophenyl isocyanate (1.54 g, 10.0 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.67 g, 10.1 mmol) and sodium hydroxide (0.406 g, 10.2 mmol) in 10 mL of 1:1 acetonitrile-water. The homogeneous solution was stirred at room temperature for 1.5 h, and then the acetonitrile removed at reduced pressure. The aqueous solution was diluted to 150 mL with water, extracted with two portions of ethyl acetate, and then acidified to pH 1 with conc. hydrochloric acid. The precipitate was filtered, washed with water, and then dried in vacuo to give 2.82 g (88%) of a white solid: mp 185-186 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.74 (s, 1 H), 7.41-7.22 (AB, 4 H, J_{AB}=8.8 Hz), 7.37-7.29 (m, 5 H), 6.84 (d, 1 H, J=8.4 Hz), 5.16-5.08 (m, 1 H), and 2.77-274 (m, 1 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.2, 154.4, 142.8, 139.4, 128.6,

128.5, 127.1, 126.4, 124.8, 119.2, 50.1 and 41.1; IR (KBr): 3336, 3304, 3064, 3032, 2928, 1706, 1652, 1595, 1553, 1493, 1398, 1312, 1240, and 704 cm^{-1}. Analysis: Calculated for $C_{16}H_{15}ClN_2O_3(H_2O)$: C, 60.05; H, 4.77; N, 8.75. Found: C, 60.05; H, 4.74; N, 8.83.

EXAMPLE 15

Preparation of N-(3-Chlorophenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 3-chlorophenyl isocyanate (1.54 g, 10.0 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.67 g, 10.1 mmol) and sodium hydroxide (0.436 g, 10.9 mmol) in 10 mL of 1:1 acetonitrile-water. The homogeneous solution was stirred at room temperature for 3 h, then concentrated at reduced pressure to afford a yellow oil. This material was dissolved in 100 mL of water, extracted with two portions of methylene chloride, and then acidified to pH 0-1 with conc. hydrochloric acid. The precipitate was filtered, washed with water, and dried in vacuo at 60 °C to give 2.86 g (90%) of a white solid: mp 172-173 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.84 (s, 1 H), 7.67 (s, 1 H), 7.37-7.29 (m, 4 H), 7.24-7.15 (m, 3 H), 6.91 (d, 2 H, J=7.8 Hz), 5.18-5.11 (m, 1 H), and 2.79-2.76 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.3, 154.4, 142.8, 142.0, 133.4, 130.4, 128.5, 127.2, 126.5, 121.0, 117.1, 116.2, 50.2, and 41.1; IR (KBr): 3392, 3064, 3032, 2928, 1717, 1653, 1592, 1552, 1483, 1424, and 700 cm^{-1}. Analysis: Calculated for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.34; H, 4.70; N, 8.82.

EXAMPLE 16

Preparation of N-(4-Methylphenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 4-methylphenyl isocyanate (1.33 g, 10.0

mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.67 g, 10.1 mmol) and sodium hydroxide (0.434 g, 10.9 mmol) in 10 mL of 1:1 acetonitrile-water. The homogeneous solution was stirred at room temperature for 2.5 h, then partially concentrated at reduced pressure. The aqueous solution was diluted with 200 mL of water, extracted with two portions of ethyl acetate, and then acidified to pH 0-1 with conc. hydrochloric acid. The precipitate was filtered, washed with water, and dried in vacuo at 60 °C to give 2.86 g (96%) of a white solid: mp 169-170 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.49 (s, 1 H), 7.38-7.20 (m, 5 H), 7.29-7.00 (AB, 4 H, J_{AB}= 8.3 Hz), 6.75 (d, 1 H, J=8.5 Hz), 5.19-5.12 (m, 1 H), 2.78-2.75 (m, 2 H), and 2.19 (s, 3 H); ^{13}C NMR(75.5 MHz; DMSO-d_6) δ 172.3, 154.7, 143.1, 137.9, 130.2, 129.3, 128.5, 127.1, 126.5, 117.9,50.1, 41.3, and 20.5; IR (KBr): 3392, 3032, 2928, 1718, 1646, 1601, 1555, 1514, 1408, 1312,1240, 1195, 816, and 712 cm^{-1}. Analysis: Calculated for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.38; H, 6.10; N, 9.37.

EXAMPLE 17

Preparation of N-(4-Trifluoromethylphenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 4-trifluoromethylphenyl isocyanate (1.87 g, 10.0 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-phenylpropionic acid (1.67 g, 10.1 mmol) and sodium hydroxide(0.414 g, 10.3 mmol)in 10 mL of 1:1 acetonitrile-water. The reaction mixture was stirred at room temperature for 4.5 h, then partially concentrated at reduced pressure. The aqueous solution was diluted with 150 mL of water and then acidified to pH 0-1 with conc. hydrochloric acid. The yellow solid that precipitated was filtered and washed with water. It was then dissolved in 150 mL of ether and extracted with three portions of aqueous sodium hydroxide. The aqueous solution was acidified to pH 0-1 with conc. hydrochloric acid. The precipitate was

filtered, washed with water, and dried in vacuo at 60 °C to give 3.18 g (90%) of a white solid: mp 172-173 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 9.12 (s, 1 H), 7.59-7.52 (AB, 4 H, J_{AB}=9 2 Hz), 7.38-7.20 (m, 5 H), 7.04 (d, 1 H, J= 8.5 Hz), 5.18-5.11 (m, 1 H), and 2.79-2.76 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.2, 154.3, 144.2, 142.8, 128.5, 127.2, 126.5, 126.1, 123.0, 121.4, 117.4, 50.2, and 41.1; IR (KBr): 3360, 3064, 3032, 2928, 1720, 1654, 1602, 1555, 1327, 1248, 1168, 1115, 1072, and 710 cm^{-1}. Analysis: Calculated for $C_{17}H_{15}F_3N_2O_3$ $(H_2O)_{0.36}$: C, 56.88; H, 4.42; N, 7.80; Found: C, 56.87; H, 4.27; N, 7.81.

EXAMPLE 18

Preparation of
N-(4-Cyanophenyl)-N'-[3-(3-(4'-methoxyphenyl)propionic acid)]urea

To a solution of p-anisaldehyde (40.8 g, 300 mmol) in 100 mL of 95:5 ethanol-water was added ammonium acetate (46.2 g, 600 mmol). The reaction mixture was warmed to 45 °C, and then treated with malonic acid (31.2 g, 300 mmol) in one portion. The resulting suspension was heated at reflux for 18 h, allowed to cool to room temperature, and filtered. The precipitate was recrystallized from 3:1 ethanol-water to give 30.9 g (53%) of a white solid 3-amino-3-(4'-methoxyphenyl)propionic acid: mp 234-235 °C; ^{1}H NMR (300 MHz; HOAc-d_4) δ 7.45-6.95 (AB, 4 H, J_{AB}=8.6 Hz), 4.76 (dd, 1 H, J=9.1, 5.2 Hz), 3.79 (s, 3 H), 3.24 (dd, 1 H, J=17.3, 9.1 Hz), and 2.97 (dd, 1 H, J=17.3, 5.2 Hz); ^{13}C NMR(75.5 MHz; HOAc-d_4) δ 176.2, 161.2, 129.7, 128.4, 115.1, 55.1, 52.8, and 38.9; IR (KBr): 3424, 2937, 2616, 1613, 1535, 1518, 1407, 1251, 1184, 1027, and 838 cm^{-1}. Analysis Calculated for $C_{10}H_{13}NO_3$: C, 61.53, H, 6.71; N, 7.18. Found: C, 61.86; H, 6.56; N, 7.10.

To a solution of 4-cyanophenyl isocyanate (1.44 g, 10.0 mmol) in 35 mL of acetonitrile was added a solution of 3-amino-3-(4'-methoxyphenyl)propionic acid (1.97 g, 10.1 mmol) and sodium

hydroxide (0.430 g, 10.8 mmol) in 10 mL of 1:1 acetonitrile-water. The resulting milky white solution was stirred at room temperature for 4 h and then partially concentrated to remove the acetonitrile. The aqueous solution was diluted with 200 mL of water and acidified to pH 1.5 with conc. hydrochloric acid. The precipitate was filtered, washed with water and ether, and then dried in vacuo to give 2.60 g (77%) of an off white solid: mp 105-107 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 9.09 (s, 1 H), 7.66-7.52 (AB, 4 H, J_{AB}=8.8 Hz), 7.28-6.87 (AB, 4 H, A=7.24, B=6.90, J_{AB}=8.7 Hz), 6.95 (d, 1 H, J=8.4 Hz), 5.09-5.02 (m, 1 H), 3.71 (s, 3 H), and 2.81-2.67 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.2, 158.3,153.8, 144.8, 134.4, 133.2, 127.6, 119.5, 117.5, 113.7, 102.6, 55.1, 49.5, and 40.9; IR (KBr): 3360, 2225, 1716, 1675, 1593, 1537, 1514, 1319, 1250, 1233, 1176, 838, and 548 cm^{-1}. Analysis: Calculated for $C_{18}H_{17}N_3O_4\ (H_2O)_{0.88}$: C, 60.87; H, 5.32; N, 11.83. Found: C, 60.84; H, 5.41; N, 12.04.

EXAMPLE 19

N-(4-Cyanophenyl)-N′-[3-(3-(2′-naphthyl)propionic acid)]urea

To a solution of 2-naphthaldehyde (15.6 g, 100 mmol) in 50 mL of 9:1 ethanol-water was added ammonium acetate (15.4 g, 200 mmol). The reaction mixture was warmed to 45 °C, and then treated with malonic acid (10.4 g, 100 mmol) in one portion. The resulting suspension was heated at reflux for 16 h, then cooled and filtered. The precipitate was recrystallized from 4:1 ethanol-water to give 14.6 g (68%) of a white solid, 3-amino-3-(2′-naphthyl)propionic acid: mp 225-227 °C; ^{1}H NMR (300 MHz; TFA-d_1) δ 7.59-7.43 (m, 4 H), 7.17-7.14 (m, 2 H), 7.07-7.05 (d, 1 H, J=7.8 Hz), 4.69 (dd, 1 H, J=10.0, 4.0 Hz), 3.18 (dd,1 H, J=18.4, 10.0 Hz), and 2.88 (dd, I H, J=18.4, 4.0 Hz); ^{13}C NMR (75.5 MHz; TFA-d_1) δ 179.2, 136.6, 135.6, 132.5, 131.9, 130.2, 130.0, 129.8, 129.5, 124.6, 56.2, and 38.5; IR (KBr): 3424, 2936, 2616, 1626,1585, 1515, 1388, 1327,1274, 823, and 745 cm^{-1}. Analysis: Calculated for $C_{13}H_{13}NO_2(H_2O)_{0.05}$: C, 72.24; H, 6.11;

N, 6.48. Found: C. 72.22; H. 6.13; N. 6.24.

To a solution of 4-cyanophenyl isocyanate (1.44 g, 10.0 mmol) in 35 mL of acetonitrile was added a slurry of 3-amino-3-(2′-naphthyl)propionic acid (2.17 g, 10.1 mmol) and sodium hydroxide (0.447 g, 11.2 mmol) in 20 mL of 1:1 acetonitrile-water. The resulting white suspension was stirred at room temperature for 2 h and then heated at reflux for 2 h. The reaction solution was partially concentrated at reduced pressure to give an aqueous suspension, which was acidified to pH 1.5 with conc. hydrochloric acid. The suspension was filtered to give 3.1 g of a pale yellow solid. This material was recrystallized from 1:1 methanol-water to afford 1.46 g (41%) of a white solid: mp 203-204 °C; ^{1}H NMR (300 MHz; DMSO-d_6): 12.39 (br s, 1 H), 9.21 (s, 1 H), 7.90-7.86 (m, 4 H), 7.67-7.56 (AB, 4 H, J_{AB}=8.8 Hz), 7.56-7.44 (m, 3 H), 7.18 (d, 1 H, J=8.4 Hz), 5.36-5.29 (m, 1 H), and 2.93-2.89 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6): 172.1, 153.9, 144.8, 140.0, 133.2, 132.8, 132.2, 128.0, 127.7, 127.5, 126.3, 125.8, 125.0, 124.7, 119.5, 117.5, 102.6, 50.2, and 40.7; IR (KBr): 3376, 3312, 2948, 2224, 1698, 1656, 1589, 1547, 1409, 1318, 1229, and 1175 cm^{-1}. Analysis: Calculated for $C_{21}H_{17}N_3O_3(H_2O)_{0.11}$: C, 69.80; H, 4.80; N, 11.63. Found: C, 69.79; H, 4.62; N, 11.64.

EXAMPLE 20

N-(4-Cyanophenyl)-N′-[3-(3-(3′,4′-dimethoxyphenyl)propionic acid)]urea

To a solution of 3,4-dimethoxybenzaldehyde (16.6 g, 100 mmol) in 50 mL of 9:1 ethanol-water was added ammonium acetate (15.4 g, 200 mmol). The reaction mixture was warmed to 45 °C, and then treated with malonic acid (10.4 g, 100 mmol) in one portion. The suspension was heated at reflux for 16.5 h, then cooled and filtered. The precipitate was washed with several portions of ether and then dried in vacuo at 60 °C to yield 12.1 g (54%) of a white solid, 3-amino-3-(3′,4′-dimethoxyphenyl)propionic acid: mp

216-217 °C; ^1H NMR (300 MHz; D_2O) δ 6.93 (s, 1 H), 6.90 (s, 2 H), 4.44 (dd, 1 H, J=8.0, 6.6 Hz), 3.72 (s, 3 H), 3.69 (s, 3 H), 2.75 (dd, 1 H, J=16.2, 6.6 Hz), and 2.64 (dd, 1 H, J=16.2, 8.0 Hz); ^{13}C NMR (75.5 MHz; AcOH-d_4) δ 176.1, 150.6, 150.2, 128.9, 120.9, 112.5, 111.6, 56.0, 53.2, and 39.0; IR (KBr): 3424, 2935, 2836, 1604, 1574, 1552, 1523, 1465, 1396, 1273, 1148, and 1025 cm^{-1}. Analysis: Calculated for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.42; H, 6.63; N, 6.15.

To a solution of 4-cyanophenyl isocyanate (1.08 g, 7.50 mmol) in 40 mL of acetonitrile was added a solution of 3-amino-3-(3′,4′-dimethoxyphenyl)propionic acid (1.71 g, 7.58 mmol) and sodium hydroxide (0.309 g, 7.72 mmol) in 5 mL of water. The reaction mixture was stirred for 3.5 h at room temperature and then partially concentrated at reduced pressure. The aqueous solution was diluted with 100 mL of water and then acidified to pH 2 with conc. hydrochloric acid, resulting in formation of a gum. The liquid was decanted and the gummy residue was dissolved with aqueous sodium hydroxide. The basic solution was washed with portions of ether and methylene chloride, then acidified to pH 2 with conc. hydrochloric acid, resulting in formation of a gum. The aqueous solution was diluted with 15 mL of methanol and then warmed gently until the gum solidified. The precipitate was filtered, washed with water, and dried in vacuo at 60 °C to give 2.00 g (72%) of a white solid: mp 148-150 °C; ^1H NMR (300 MHz; DMSO-d_6) δ 12.30 (br s, 1 H), 9.11 (s, 1 H), 7.66-7.53 (AB, 4 H, J_{AB}=8.8 Hz), 6.99-6.83 (m, 4 H), 5.09-5.02 (m, 1 H), 3.74 (s, 3 H), 3.71 (s, 3 H), and 2.76-2.73 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.2, 153.8, 148.6, 147.9, 144.9, 135.0, 133.2, 119.5, 118.3, 117.5, 111.7, 110.5, 102.6, 55.6, 49.9, and 41.1; IR (KBr): 3360, 2224, 1704, 1594, 1518, 1411, 1319, 1233, 1145, 1024, 848, and 552 cm^{-1}. Analysis: Calculated for $C_{19}H_{19}N_3O_5$ $(H_2O)_{0.86}$: C, 59.30; H, 5.43; N, 10.92. Found: C, 59.27; H, 5.07; N, 10.88.

EXAMPLE 21

Preparation
of N-(4-Cyanophenyl)-N′-[3-(3-(3′-4′-methylenedioxyphenyl)
propionic acid)]urea

To a solution of piperonal (15.0 g, 100 mmol) in 50 mL of 9:1 ethanol-water was added ammonium acetate (15.4 g, 200 mmol). The reaction mixture was warmed to 45 °C, and then treated with malonic acid (10.4 g, 100 mmol) in one portion. The suspension was heated at reflux for 16 h, cooled to 0 °C, and filtered. The precipitate was washed with ethanol and ether, and then dried in vacuo at 60 °C to give 7.32 g (ca 35%) of a yellow solid. This material consisted of a 91:9 mixture of the desired β-amino acid [3-amino-3-(3′,4′-methylenedioxyphenyl)propionic acid] and an α,β-unsaturated acid; it was used in the next reaction without further purification. ^{1}H NMR (300 MHz; AcOH-d_4): 7.01 (s, 1 H), 6.99-6.82 (AB, 2 H, J_{AB}=8 0 Hz), 5.97 (s, 2 H), 4.75 (dd, 1 H, J=9.1, 5.4 Hz), 3.23 (dd, 1 H, J=17.3, 9.1 Hz), and 2.97 (dd, 1 H, J=17.3, 5.4 Hz).

To a solution of 4-cyanophenyl isocyanate (1.08 g, 7.50 mmol) in 40 mL of acetonitrile was added a solution of 3-amino-3-(3′,4′-methylenedioxyphenyl)propionic acid (1.81 g, 7.88 mmol) and sodium hydroxide (0.360 g, 9.00 mmol) in 5 mL of water. The suspension was stirred at room temperature for 1.25 h and then filtered. The solid was suspended in 50 mL of water and the solution acidified to pH 2 with conc. hydrochloric acid. The precipitate was filtered, washed with water, and dried in vacuo at 60 °C to give 1.73 g (65%) of a white solid: mp 189-191 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 12.3 (br s, 1 H), 9.14 (s, 1 H), 7.66-7.52 (AB, 4 H, J=8.7 Hz),7.00 (d, 1 H, J=8.4 Hz), 6.93 (s, 1 H), 6.86-6.81 (m, 2 H), 5.97 (s, 2 H), 5.06-4.98 (m, 1 H),and 2.80-2.65 (m, 2 H); ^{13}C NMR (75.5 MHz; DMSO-d_6) δ 172.1, 153.8, 147.3, 146.2, 144.8,136.6, 133.2, 119.6, 119.5, 117.5, 108.0, 107.0, 102.6, 101.0, 49.9, and 41.0; IR (KBr):3060, 2225, 1714, 1675,

1593, 1537, 1505, 1444, 1412, 1317, 1238, 1176, 1040, 840, and 552 cm^{-1}. Analysis: Calculated for $C_{18}H_{15}N_3O_5$ $(H_2O)_{0.80}$: C, 58.79; H, 4.55; N, 11.43. Found: C, 58.77; H, 4.30; N, 11.40.

EXAMPLE 22

Preparation of N-(4-Cyanophenyl)-N'-[3-(3-cyclooctylpropionic acid)]urea

A suspension of 3-amino-3-cyclooctylpropionic acid (1.99 g, 10.0 mmol) and 4-cyanophenyl isocyanate (1.44 g, 10.0 mmol) in 100 mL of acetonitrile was stirred for two hours at room temperature. The reaction mixture was then heated at reflux until a clear solution formed. The solution was allowed to cool and stirred overnight at room temperature. The reaction mixture was filtered to yield a crude product which was slurried in ether, filtered, and dried to a constant weight of 3.1 g (90%) of a white solid: IR (KBr) cm^{-1} 3360, 3100, 2920, 2380, 2240, 1760, 1680, 1600, 1540; ^1H NMR (DMSO-d_6) δ 8.9 (s, 1H), 7.5 (dd, 4H, J=9.7Hz, J=28.6Hz), 6.0 (d, 1H, J=9.2Hz), 3.9 (m, 1H), 2.4 (dd, 2 H, J=4.6, J=14.6Hz), 1.2-1.8 (m, 15H); ^{13}C NMR (DMSO-d_6) δ 176.5, 157.7, 148.5, 136.7, 123.0, 120.8, 105.9, 55.4, 40.7, 33.0, 31.5, 30.0, 29.6, 29.4, 28.7. Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.12. Found: C, 66.39; H, 7.21; N, 12.24.

EXAMPLE 23

Preparation of N-(4-Cyanophenyl)-N'-[3-(3-phenylpropionic acid)]thiourea.

To a stirred suspension of 4-cyanophenyl isothiocyanate (1.60 g, 10.0 mmol) and 3-amino-3-phenylpropionic acid (1.65 g, 10.0 mmol) in 50 mL of acetonitrile was added 10 mL of 1 N NaOH. The clear yellow solution which immediately formed was stirred overnight and the solvent then removed under reduced pressure. The residue was dissolved in 50 mL of 1:1 ethyl acetate/water and

the aqueous layer was extracted twice with 50 mL ethyl acetate. The product was precipitated from the aqueous layer as a gum after adjusting the pH to 2.5 with 4 N HCl. The gummy product was stirred overnight in water to produce a fluffy white solid. The solid was isolated by filtration and dried to yield 2.65 g (82%) of the desired product as a off-white powder: IR (KBr) cm^{-1} 3320, 3150, 2235, 1733, 1604, 1542, 1519, 1509,1169; ^1H NMR (DMSO-d_6) δ 10.2 (s, 1H), 8.7 (d, 1H, J=8.3Hz), 7.7 (dd, 4H, J=8.3, J=24Hz), 7.2-7.5 (m, 5H), 5.8 (q, 1H, J=7.3Hz), 2.9 (dd, 2H, J=7.3, J=16Hz); ^{13}C NMR (DMSO-d_6) δ 184.6, 177.0, 149.3, 146.3, 137.8, 133.4, 132.3, 131.9, 126.3, 124.2, 109.9, 59.1. Anal. Calc. for $C_{17}H_{15}N_3SO_2$: C,62.75; H,4.65; N,12.91. Found: C,62.60; H,4.78; N,12.61.

EXAMPLE 24

Preparation of N-(4-Cyanophenyl)-N′-[3-(3-(3-quinolyl)propionic acid)]urea

To a stirred suspension of 4-cyanophenyl isocyanate (1.0 g, 7.0 mmol) and 3-amino-3-(3-quinolyl)propionic acid (1.0 g, 4.6 mmol) in 50 mL of acetonitrile was added 5 mL of 1 N NaOH. The reaction mixture was stirred overnight before the solvent was removed at reduced pressure. The residue was dissolved in 100 mL of equal parts of ethyl acetate and water. The aqueous layer was washed with 50 mL of ethyl acetate and stripped under vacuum to remove traces of ethyl acetate. The pH of the solution was adjusted to 4 with diluted HCl where an oil separated out. The oil was stirred overnight in 25 mL of fresh water. The thick oil was placed in a vacuum oven and thoroughly dried to a glassy solid (525 mg, 31%): IR (KBr) cm^{-1} 3360, 3060, 2222, 1703, 1594, 1583, 1317,1226; ^1H NMR (DMSO-d_6) δ 9.3 (m, 1H), 9.0 (s, 1H), 8.4 (s, 1H), 7.9 (t, 2H, J=7.8Hz), 7.7 (t, 1H, J=7.8Hz), 7.6 (m, 3H), 7.5 (d, 2H, J=8.7Hz), 7.3 (d, 1H, J=8.7Hz), 5.4 (q, 1H), 3.0 (d, 2H, J=6.8Hz): ^{13}C NMR (DMSO-d_6), δ 173.0, 155.2, 150.3, 146.0, 145.9, 137.0, 136.1, 134.4, 132.2, 129.4, 128.7, 128.4, 120.8,

118.7, 103.9, 49.5. Anal. Calcd for $C_{20}H_{16}N_4O_3(1.25H_2O)$: C,62.74; H,4.87; N,14.63. Found: C,62.72; H,4.84; N,14.28.

EXAMPLE 25

Preparation of N-(4-Methoxycarbonylphenyl)-N'-[3-(3-phenylpropionic acid)]thiourea

To a stirred suspension of 4-methoxycarbonylphenyl isothiocyanate (1.93 g, 10.0 mmol) and 3-amino-3-phenylpropionic acid (1.65 g, 10.0 mmol) in 60 mL of acetonitrile was added 10 mL of 1 N NaOH. The yellow solution was stirred for one hour before the solvent was removed under vacuum. The residue was dissolved in 200 mL of 50/50 ethyl acetate:water and the aqueous phase extracted with ethyl acetate (2 x 100 mL). The product was separated from the aqueous layer as a gum after adjusting the pH to 2 with 1 N HCl. The gum was stirred in water over the weekend and the product (2.0 g, 55%) isolated by filtration as a fine white powder: mp 144-6°C; ^1H NMR (DMSO-d_6) δ 10.0 (s, 1H), 8.6 (s, 1H), 7.9 (d, 2H, J=8.7Hz) 7.4 (m, 5H), 5.9 (q, 1H, J=6.8Hz), 3.8 (s, 1H), 2.9 (dd, 2H, J=6.8, J=16.5Hz); ^{13}C NMR (DMSO-d_6) δ 184.2, 176.6, 170.5, 148.9, 145.9, 134.5, 132.9, 131.7, 131.4, 128.6, 125.4, 58.6, 56.6, 44.6. Anal. Calcd for $C_{18}H_{18}N_2O_4S(0.25 H_2O)$: C,59.45; H,5.15; N,7.70. Found: C,59.44; H,5.06; N,7.62.

EXAMPLE 26

Preparation of N-(4-Cyanophenyl)-N'-[3-(3-cyclohexylpropionic acid)]urea

A suspension of 3-amino-3-cyclohexanepropionic acid (2.27 g, 13.2 mmol) and 4-cyanophenyl isocyanate (1.90 g, 13.2 mmol) in 100 mL of acetonitrile was stirred for 1 hour. The reaction mixture was then heated at reflux until a clear solution formed. The solution was allowed to cool and stirred overnight at room

temperature. The cooled reaction mixture was filtered to yield a white solid which was dried to constant weight under vacuum. The crude product was stirred in 1 N NaOH, filtered, and the filtrate extracted with $CHCl_3$ (3 x 50 mL). The pH of the filtrate was adjusted to 2 with concentrated HCl and the resulting white solid isolated by filtration. After drying, the solid was recrystallized from 125 mL of acetonitrile to yield 2.1 g (50%) of the desired product as a white crystalline solid: IR (KBr) cm^{-1} 3320, 2940, 2860, 2240, 1720, 1680, 1600, 1540; ^1H NMR (DMSO-d_6) δ 8.6 (s, 1H), 7.1-7.3 (dd, 4H, J=8.3 Hz, J=30.5Hz), 6.0 (d, 1H, J=9.2Hz),3.5 (m, 1H), 1.9-2.2 (m, 2H), 0.5-1.4 (m, 11H); ^{13}C NMR (DMSO-d_6) δ 173.5, 154.7, 145.5, 133.7, 120.0, 117.8, 102.8, 51.2, 41.8, 37.6, 29.8, 28.7, 26.5, 26.3, 26.3. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.745; H, 6.712; N, 13.324. Found: C, 64.67; H, 6.73; N, 13.49.

EXAMPLE 27

Preparation of
N-(4-Cyanophenyl)-N'-[3-(3-(3'-nitrophenyl)propionic acid)]urea

To a solution of 4-cyanophenyl isocyanate (2.16 g, 15.0 mmol) in 50 mL of acetonitrile was added a solution of 3-amino-3-(3'-nitrophenyl)propionic acid (2.10 g, 15.0 mmol) in 25 mL of water and 10.0 mL of 1 N NaOH. The reaction mixture was stirred overnight at room temperature before the solvents were removed at reduced pressure. The residue was dissolved in 75 mL of ethyl acetate and 75 mL of water and the ethyl acetate phase extracted with 0.1 N NaOH (2 x 100mL). The combined aqueous extracts were acidified with 4 N HCl and the desired product isolated by filtration (0.83 g, 23%) as a white fluffy powder: mp 173-6°C; IR (KBr) cm^{-1} 3380, 3100, 2225, 1722, 1683, 1662, 1594, 1532, 1411, 1351, 1320,1238; ^1H NMR (DMSO-d_6) δ 9.3 (s, 1H), 8.3 (s, 1H), 8.1 (d, 1H, J=7.5Hz), 7.8 (d, 1H, J=7.3Hz), 7.5-7.7 (m, 5H), 7.3 (d, 1H, J=7.3Hz), 5.2 (q, 1H, J=7.3Hz), 2.9 (d, 2H, J=6.1Hz); ^{13}C NMR (DMSO-d_6) δ 171.8, 154.1, 148.1, 145.3, 144.7,

133.6, 133.3, 130.0, 122.2, 121.1, 119.4, 117.8, 112.5, 49.4. Anal. Calcd for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.08; H, 4.05; N, 15.56.

EXAMPLE 28

Preparation of N-(4-Cyanophenyl)-N'-[3-(3-(4-pyridylpropionic acid)]urea Sodium salt

To a stirred suspension of 3-amino-3-(4-pyridyl)propionic acid (0.17 g, 1.0 mmol) and 4-cyanophenyl isocyanate (0.45 g, 3.0 mmol) in 25 mL of acetonitrile was added 1.0 mL of 1 N NaOH and 5 mL of water. The clear solution was stirred for one hour before the solvents were removed at reduced presssure. The residue was dissolved in 75 mL of 50/50 ethyl acetate:water and the aqueous phased washed with ethyl acetate (2 x 50mL). The crude product (0.32 g) was isolated by lyophilization of the aqueous phase and purified by reverse phase chromatography to yield 0.12 g (36%) of a white powder: ^{1}H NMR (DMSO-d_6) δ 9.25 (bs, 1H), 8.4 (d, 2H, 5.8Hz), 7.7 (d, 2H, J=8.7Hz), 7.5 (d, 2H, J=8.7Hz), 7.3 (d, 2H, J=5.8Hz), 5.0 (q, 1H, J=5.8Hz), 2,4 (m, 2H); ^{13}C NMR δ 174.2, 155.0, 154.6, 149.2, 146.5, 132.7, 121.5, 119.6, 117.3, 101.2, 51.5, 44.6.

EXAMPLE 29

Preparation of N-(4-Carboxyphenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a stirred solution of NaOH (0.224 g, 5.60 mmol) in 20 mL of 1/1 MeOH/water was added to the urea prepared in Example 1. (0.500 g, 1.40 mmol). After 3 h, the reaction mixture was partially concentrated to remove the MeOH. The reaction mixture was diluted to a volume of 50 mL with water and acidified with 6 mL of 1 N HCl. The precipitate was isolated by filtration and air-dried to afford 0.44 g (96%) of the urea as a white powder:

mp 190-195 °C; ^{1}H NMR ($DMSO-d_6$) δ 12.43 (br s, 2 H), 9.0 (s, 1 H), 7.9-7.74 (m, 2 H), 7.55-7.2 (m, 7 H), 6.96 (d, J= 8.4 Hz, 2 H), 5.2-5.05 (m, 1 H), 2.9-2.7 (m, 2 H); ^{13}C NMR ($DMSO-d_6$) δ 172.0, 167.0, 153.9, 144.6, 142.6, 130.5, 128.3, 127.0, 126.3, 122.9, 116.6, 49.9, 40.8; IR(KBr) cm^{-1} 3460, 3080, 3040, 1700, 1590, 1500, 1390, 1310, 1280, 1240, 1175. Anal. Calcd for $C_{17}H_{16}N_2O_5$-(0.13 H_2O): C, 61.72; H, 4.96; N, 8.47. Found: C, 61.71; H, 4.87; N, 8.73.

EXAMPLE 30

Preparation of N-(Phenyl)-N'-[3-(3-phenylpropionic acid)]urea

The urea was prepared analogously to N-(4-bromophenyl)-N'-(2-carboxy-1-phenylethyl)urea except phenyl isocyanate was substituted for 4-bromophenyl isocyanate to afford 2.69 g (91%) of the urea as a powder: mp 179-180 °C; ^{1}H NMR ($DMSO-d_6$) δ 12.30 (br s, 1 H, NH), 8.58 (s, 1 H), 7.6-7.1 (m, 8 H), 7.0-6.75 (m, 2 H), 5.17-5.10 (overlapping dt, 1 H), 2.9-2.7 (m, 2 H); ^{13}C NMR ($DMSO-d_6$) δ 172.1, 154.4, 142.9, 140.3, 128.7, 128.4, 126.9, 126.3, 121.2, 117.6, 49.9, 41.1; IR (KBr) cm^{-1} 3360, 3060, 3020, 1718, 1640, 1600, 1560, 1500, 1460, 1400, 1310, 1240. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.58; N, 9.76.

EXAMPLE 31

Preparation of N-(4-Formylphenyl)-N'-[3-(3-phenylpropionic acid)]urea

To a stirred solution (slightly cloudy) of 1,1'-carbonyldiimidazole (5.27 g, 32.5 mmol) and imidazole (3.32 g, 48.7 mmol) in 50 mL of dry THF cooled in an ice bath was added a solution of methyl 3-amino-3-phenylpropionate (5.82 g, 32.5 mmol) in 10 mL of THF over 15 minutes. The reaction solution was stirred an additional 15 minutes, then a solution of 4-

aminobenzyl alcohol (4.00 g, 32.5 mmol) in 25 mL of THF was rapidly added. After an additional 30 minutes, the cooling bath was removed and the reaction mixture was stirred for 17 hours. The reaction mixture was then concentrated, the residue dissolved in 100 mL of CH_2Cl_2 and washed with water (100 mL). The aqueous wash was extracted with CH_2Cl_2 (50 mL) and the organic layers combined, dried ($MgSO_4$), and concentrated to afford 9.27 g of crude product. The crude product was purified by flash chromatography (silica gel, 4-6% MeOH/CH_2Cl_2) to afford 3.5 g (33%) of N-(4-hydroxymethylphenyl)-N′-[3-(methyl 3-phenylpropionate)]urea as a very pale yellow solid: mp 108-118 °C; TLC (1/9 CH_3OH/CH_2Cl_2, UV) R_f= 0.44; ^1H NMR (DMSO-d_6) δ 7. 69 (s, 1 H, NH), 7.03, 7.98 (AB quartet, J= 8.6 Hz, 4 H), 7.3-7.1 (m, 5 H), 6.48 (d, J= 8.3 Hz, 1 H, NH), 5.35-5.2 (m, 1 H), 4.38 (s, 2 H, CH_2O), 3.5 (s, 3 H, CO_2CH_3), 2.85-26 (m, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 171.7, 155.5, 141.3, 138.1, 135.2, 128.6, 127.7, 127.4, 126.1, 119.8, 64.4, 51.8, 50.6, 41.0; IR (KBr) cm^{-1} 3340 (br), 1735, 1690, 1660, 1600, 1550, 1513, 1440, 1418. Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.94; H, 6.20; N, 8.84.

To a stirred solution of N-(4-hydroxymethylphenyl)-N′-[3-(methyl 3-phenylpropionate)]urea (2.30 g, 7.01 mmol) in 230 mL of CH_2Cl_2 was added MnO_2 (3.00 g, 34.5 mmol) as a solid in one portion. The reaction suspension was stirred for 44 h, then filtered through celite. The filtrate was concentrated and the residue purified by flash chromatography (3/7 EtOAc/hexane, silica gel) to afford 1.14 g (50%) of the desired N-(4-Formylphenyl)-N′-[3-(methyl 3-phenylpropionate)]urea. An additional 0.518 g (23%) of material was obtained from copious washing of the celite cake with CH_2Cl_2, CH_3CN, and EtOH followed by flash chromatography purification: TLC (0.5/9.5 CH_3OH/CH_2Cl_2, UV) R_f= 0.38; ^1H NMR (DMSO-d_6) δ 9.79 (s, 1 H, CHO), 9.11 (s, 1 H), 7.76 (d, 2 H, J= 8.6 Hz), 7.57 (d, 2 H, J= 8.6 Hz), 7.4-7.2 (m, 5 H), 7.02 (d, 1 H, J= 8.4 Hz, CHN<u>H</u>), 5.18-5.10 (m, 1 H, CH), 3.54 (s, 3 H, CO_2CH_3), 2.95-2.82 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ

191.3, 170.9, 153.8, 146.2, 142.1, 131.1, 129.6, 128.4, 127.2, 126.3, 117.0, 51.5, 50.0, 40.6; IR (KBr) cm^{-1} 3370, 3320, 1727, 1687, 1669, 1595, 1560, 1544, 1435, 1365, 122, 1165; TLC (3/7 EtOAc/hexane) R_f= 0.48. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 65.70; H, 5.61; N, 8.51. Found: C, 65.68; H, 5.47; N, 8.12.

To a stirred suspension of N-(4-formylphenyl)-N-[3-(methyl 3-phenylpropionate)]urea (1.14 g, 3.49 mmol) in 230 mL of MeOH and 50 mL of water was added 14 mL of 1 N NaOH (14 mmol). The reaction mixture became homogeneous after 1 h. After 3.5 hours, the reaction solution was concentrated to remove the MeOH, and diluted to a total volume of 250 mL with water. This solution was washed with EtOAc (100 mL). The aqueous layer was partially concentrated to remove traces of EtOAc and the pH adjusted to 1 with 17 mL of 1 N HCl. A gum formed and the suspension was stirred overnight. The gum had solidified and the resulting solid was isolated by filtration. The white powder was dried in vacuo (<0.2 mm, 40 °C) to afford 1.06 g (97%) of the desired urea : mp 145-148 °C; ^1H NMR (DMSO-d_6) δ 12.35 (br s, 1 H), 9.79 (s, 1 H, CHO), 9.15 (s, 1 H, NH), 7.76 (d, 2 H, J= 8.5 Hz), 7.57 (d, 2 H, J= 8.5 Hz), 7.45-7.2 (m, 5 H, Ph), 7.04 (d, 1 H, J= 8.4 Hz), 5.2-5.05 (m, 1 H), 2.9-2.7 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 191.5, 191.0, 172.0, 153.8, 146.2, 142.5, 131.1, 129.6, 128.4, 126.4, 117.0, 50.0, 40.8; IR (KBr) cm^{-1} 3400, 3360, 3060, 1720, 1690, 1673, 1660, 1560, 1540, 1166. Anal. Calcd for $C_{17}H_{16}N_2O_4$-(0.11 H_2O): C, 64.93; H, 5.21; N, 8.91. Found: C, 64.90; H, 5.10; N, 8.85.

EXAMPLE 32

Preparation of N-(4-Hydroxymethylphenyl-N'-[3-(3-phenylpropionic acid)]urea

To a stirred solution of N-(4-hydroxymethylphenyl)-N'-[3-(methyl 3-phenylpropionate)]urea prepared as in Example 31, (0.500 g, 1.52 mmol) in 25 mL of CH_3OH was added 5 mL of 1 N NaOH

and 5 mL of water. Reaction progress was monitored by HPLC. After 1.5 h, the reaction mixture was partially concentrated to remove the CH_3OH. The reaction mixture was then diluted with 20 mL of water and acidified with 5 mL of 1 N HCl. A gum formed upon acidification. The reaction mixture was diluted with 5 mL of CH_3OH and the reaction mixture was stirred overnight. The resulting slurry was filtered to yield after air-drying 0.35 g (73%) of the urea as a flocculent white powder: mp 138-140 °C; ^1H NMR (DMSO-d_6) δ 12.3 (br s, 1 H, COOH), 8.54 (s, 1 H, NH), 7.45-7.1 (m, 9 H, Ar and Ph), 6.75 (d, J= 8.5 Hz, 1 H), 5.11(apparent q, 1 H), 5.01 (br s, 1 H), 4.38 (s, 2 H), 2.85-2.65 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.1, 154.4, 142.9, 139.0, 135.2, 128.4, 127.2, 127.0, 126.4, 117.4, 62.8, 50.0, 41.1; IR (KBr) cm^{-1} 3400, 3340, 1710, 1660, 1550, 1420, 1320, 1240. Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.70; H, 5.59; N, 8.78.

EXAMPLE 33

Preparation of N-(4-Cyanophenyl)-N'-[3-(3-(3'-hydroxy-4'-methoxyphenyl) propionic acid)]urea

A stirred suspension of 3-hydroxy-4-methoxybenzaldehyde (15.2 g, 100 mmol) and NH_4OAc (15.4 g, 100 mmol) in a mixture of 45 mL of EtOH and 5 mL of water was heated to 45 °C. Malonic acid (10.4 g, 100 mmol) was added as a solid and the resulting mixture was refluxed for 19 h. The cooled reaction suspension was filtered and the solid washed with copious amounts of EtOH to afford 12.59 g (59%) of crude product as a ivory powder. The crude product (10.0 g) was slurried in hot EtOH and filtered. The solid was air-dried to afford 8.5 g (40%) of 3-amino-3-(3'-hydroxy-4'-methoxyphenyl)propionic acid as a white powder: mp 215-217 °C; ^1H NMR (D_2O) δ 7.1-6.9 (m, 3 H), 4.6-4.5 (m, 1 H), 3.85 (s, 3 H), 2.95-2.7 (m, 2 H); ^{13}C NMR (D_2O) δ 178.6, 149.3, 146.4, 130.4, 120.9, 115.4, 114.0, 57.2, 53.6, 41.7. Anal. Calcd for

$C_{10}H_{13}N_1O_4$: C, 56.90; H, 6.20; N, 6.63. Found: C, 56.57, H, 6.19; N, 6.75.

To a stirred suspension of 4-cyanophenyl isocyanate (1.44 g, 10.0 mmol) in 25 mL of CH_3CN was rapidly added a solution of 3-amino-3-(3'-hydroxy-4'-methoxyphenyl)propionic acid (2.11 g, 10.0 mmol) and NaOH (0.40 g, 10 mmol) in 20 mL of 1/1 CH_3CN/water. After 17 h, the reaction mixture was partially concentrated to remove the CH_3CN. The reaction mixture was then diluted with 75 mL of water and washed with EtOAc (2 x 50 mL ea.). The pH of the reaction mixture was adjusted to 0-1 with 11 mL of 1 N HCl. A gum formed upon acidification and the aqueous layer was decanted from the gum and the gum washed with water. The gum was slurried in $CHCl_3$ (100 mL) and stirred overnight. The resulting powder was isolated by filtration. This solid was dissolved in EtOH (100 mL) and concentrated to a thick oil. The oil was slurried in 100 mL of refluxing $CHCl_3$. The cooled suspension was filtered and the solid air-dried to afford 2.6 g (73%) of the urea as an off-white solid: ^1H NMR (DMSO-d_6) δ 12.3 (br s, 1 H), 9.1 (s, 1 H), 8.94 (s, 1 H), 7.64 (d, 2 H, J= 8.7 Hz), 7.54 (d, 2 H, J= 8.7 Hz), 7.0-6.7 (m, 4 H), 5.02-4.95 (m, 1 H), 3.72 (s, 3 H), 2.8-2.6 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 172.1, 153.8, 146.7, 146.3, 144.8, 135.0, 133.3, 119.5, 117.5, 117.0, 113.9, 112.4, 102.5, 55.7, 49.5, 41.0; IR (KBr) cm^{-1} 3370, 2225, 1720, 1700, 1680, 1600, 1540, 1510. Anal. Calcd for $C_{18}H_{17}N_3O_5$-(0.11 H_2O): C, 58.60; H, 4.10; N, 11.39. Found: C, 58.58; H, 4.40; N, 11.32.

EXAMPLE 34

Preparation of N-(4-Cyanophenyl)-N'-(3-nonanoic acid)urea

A solution of methyl trans-2-nonenoate (3.40 g, 20.0 mmol) and benzyl amine (2.2 mL, 2.1 g, 20 mmol) in 50 mL of MeOH was stirred for 12 days at RT. The reaction progress was monitored by TLC (1/1 EtOAc/hexane, UV). The reaction solution was then refluxed for 1 h with no observable change by TLC. The reaction mixture was concentrated and the crude adduct was purified by

flash chromatography (2.5/7.5 EtOAc/hexane) to afford 4.00 g (72%) of methyl N-benzyl 3-aminononanoate as an oil: TLC (2.5/7.5 EtOAc/hexane) R_f = 0.35; ^{1}H NMR ($CDCl_3$) δ 7.4-7.2 (m, 5 H), 3.78 (s, 2 H), 3.67 (s, 3 H), 3.03 (p, 1 H, J= 6.2 Hz), 2.46 (d, 2H, J= 6.2 Hz), 1.65-1.2 (m, 10 H), 0.88 (br t, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 140.5, 128.3, 128.1, 126.8, 54.2, 51.5, 51.4, 51.0, 50.9, 50.8, 39.1, 34.3, 31.7, 29.3, 25.6, 22.6, 14.0.

To a solution of methyl N-benzyl 3-aminononanoate (3.50 g, 12.6 mmol) in 35 mL of ethanol was added 100 mg of 5% Pd/C and the resulting suspension was treated with 50 psi of H_2 in a Parr Type Shaker. After 3 h, 100 mg of 20% $Pd(OH)_2$/C was added and the hydrogenolysis was continued for 19 h. The reaction mixture was then filtered through celite to remove the catalysts and concentrated to afford 2.43 g (100%) of a pale yellow oil which was a 79/21 mixture of methyl and ethyl 3-aminononanoate respectively. Methyl ester: ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3 H), 3.25-3.15 (m, 1 H), 2.47 (dd, J= 4.0 Hz, 15.6 Hz, 1 H), 2.26 (dd, 1 H, J= 9.0 Hz, 15.6 Hz), 1.6-1.2 (m, 12 H), 0.9-0.8 (m, 3 H). This mixture was used directly in the next reaction.

To a stirred solution of methyl 3-aminononanoate and ethyl 3-aminononanoate (80/20, 2.00 g, 10.4 mmol) in 35 mL of ethyl acetate was added 4-cyanophenyl isocyanate (1.50 g, 10.4 mmol) in one portion as a solid. The resulting suspension was stirred for 7 h. The reaction mixture was filtered and the solid washed with ether (50 mL) and air-dried to afford 2.91 g (84%) of a 79/21 mixture of the desired compounds, N-(4-cyanophenyl)-N'-[3-(methyl nononoate)]urea and N-(4-cyanophenyl)-N'-[3-(ethyl nonanoate)]urea as a white powder. Methyl ester: ^{1}H NMR (DMSO-d_6) δ 9.01 (s, 1 H), 7.68 (d, J= 8.8 Hz, 2 H, Ar), 7.58 (d, J= 8.8 Hz, 2 H, Ar), 6.36 (d, J= 8.7 Hz, 1 H), 4.05- 3.92 (m, 1 H), 3.61 (s, 3 H, CO_2CH_3), 2.53-2.47 (m, 2 H, $CHCO_2$), 1.55-1.15 (m, 10 H), 0.87 (apparent t, 3 H);^{13}C NMR (DMSO-d_6) δ 171.5, 154.1, 144.9, 133.2, 119.4, 117.4, 102.3, 51.3, 46.3, 39.3, 34.1, 31.2, 28.5, 25.4, 22.0, 14.0.

To a stirred suspension of a 79/21 mixture of N-(4-cyanophenyl)-N′-[3-(methyl nonanoate)]urea and N-(4-cyanophenyl)-N′-[3-(ethyl nonanoate)]urea (2.50 g, 7.52 mmol) in a mixture of methanol (100 mL) and water (25 mL) was added 30 mL of 1 N NaOH. The reaction progress was monitored by HPLC. The reaction was complete after 21 h, the methanol was removed **in vacuo** and the resulting slurry diluted with 150 mL of water. This slurry was filtered and the solid was washed with water. The solid was dried in vacuo to yield 2.07 g (81%) of the urea as a white powder: mp >230 °C; ^1H NMR (DMSO-d_6) δ 10.82 (s, 1 H), 7.9-7.6 (m, 1 H), 7.70 (d, 2 H, J= 8.8 Hz), 7.53 (d, 2 H, J= 8.8 Hz), 3.9-3.7 (m, 1 H), 2.3-2.05 (m, 2 H), 1.6-1.45 (m, 2 H), 1.8 (br s, 8 H), 0.8 (apparent t, 3 H); ^{13}C NMR (DMSO-d_6) δ 176.1, 154.8, 146.4, 132.8, 119.8, 117.3, 100.9, 34.8, 31.4, 28.9, 26.0, 22.1, 13.9. Anal. Calcd for $C_{17}H_{22}N_3O_3Na$-(0.9 H_2O): C, 57.42; H, 6.75; N, 11.82. Found: C, 57.39; H, 6.49; N, 11.83.

EXAMPLE 35

Preparation of N-(4-Formylphenyl)-N′-[3-(3-(3-pyridyl)propionic acid)]urea

To a cooled (4 °C) stirred solution of 1,1′-carbonyldiimidazole (3.24 g, 20.0 mmol) and imidazole (2.04 g, 30.0 mmol) in 65 mL of THF was added a solution of methyl 3-amino-3-(3-pyridyl)propionate (3.60 g, 20.0 mmol) in 25 mL of THF over 10 minutes. After stirring an additional 15 minutes, the cooling bath was removed. After 45 minutes, a solution of 4-aminobenzaldehyde (2.42 g, 20.0 mmol) in 100 mL of THF was rapidly added to the reaction solution. The reaction mixture was then heated to reflux for 24 h. The reaction mixture was concentrated and the residue purified by flash chromatography (silica gel, 6.5/93.5 CH_3OH/ CH_2Cl_2) to afford 5.01 g of crude product. The crude product was purified by flash chromatography (silica gel, 0.5/9.5 CH_3OH/ CH_2Cl_2) to afford 3.41 g (52%) of

N-(4-formylphenyl)-N-[3-(methyl 3-(3-pyridyl)propionate)]urea as yellow foam. A small sample was recrystallized from EtOAc for analysis, the remainder was used directly in the next reaction. ^1H NMR (DMSO-d_6) δ 9.79 (s, 1 H), 9.16 (s, 1 H), 8.59 (s, 1 H), 8.46 (d, J- 3.1 Hz, 1 H), 7.9-7.7 (m, 3 H), 7.65-7.5 (m, 2 H), 7.37 (dd, J= 4.8, 7.9 Hz, 1 H), 7.12 (s, J= 8.2 Hz, 1 H), 5.25-5.15 (m, 1 H), 3.56 (s, 3 H), 3.35-2.90 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 191.4, 171.3, 154.4, 148.6, 147.5, 245.5, 137.3, 135.0, 131.4, 130.7, 123.9, 118.0, 52.0, 48.4, 39.8. Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.24; N, 12.84. Found: C, 62.01; H, 5.18; N, 12.65.

To a stirred suspension of N-(4-formylphenyl)-N'-[3-(methyl 3-(3-pyridyl)propionate)]urea in 90 mL of a 5/4 mixture of MeOH and water was added 7.60 mL of 1 N HCl followed by 15.2 mL of 1 N NaOH. After 26 h, the reaction mixture was partially concentrated to remove the MeOH, and diluted with 50 mL of water. The reaction solution was then washed with CH_2Cl_2 (3 x 50 mL ea.). The aqueous layer was decolorized with Norit A and filtered through celite and lyophilized. The residue was dissolved in 100 mL of ethanol and filtered to remove the insoluble NaCl. The filtrate was concentrated, the residue dissolved in 25 mL of water and lyophilized. The residue was purified by reverse phase chromatography and lyophilized to afford 1.92 g (76%) of the urea as a white powder: mp 200-205 °C decomp; ^1H NMR (D_2O) δ 9.71 (s, 1 H, CHO), 8.54 (s, 1 H), 8.42 (d, J= 4.9 Hz, 1 H), 7.9-7.7 (m, 3 H), 7.6-7.4 (m, 3 H), 5.14 (t, J= 7 Hz, 1 H), 2.8-2.65 (m, 2 H): ^{13}C NMR (D_2O) δ 194.7, 178.3, 155.8, 147.5, 146.7, 145.4, 138.5, 135.1, 131.6, 129.9, 124.2, 118.3, 50.1, 43.7. Anal. Calcd for $C_{16}H_{14}N_3O_4Na_1$-(0.16 H_2O): C, 56.83; H, 4.27; N, 12.43. Found: C, 56.80; H, 4.27; N, 12.43.

EXAMPLE 36

Preparation of N-(4-Cyanophenyl)-N′-[3-(4-phenylbutanoic acid)]urea sodium salt

A stirred suspension of phenylacetaldehyde (6.08 g, 50.6 mmol) and methyl (triphenylphosphoranylidene)-acetate in 150 mL of CH3CN was heated to reflux for 1.75 h. Reaction progress was monitored by TLC (1/9 EtOAc/hexane). The reaction mixture was concentrated and the residue slurried in 100 mL of 0.8/9.2 EtOAc/hexane. The slurry was filtered to remove excess Wittig reagent and triphenylphosphine oxide. The filtrate was concentrated and purified by flash chromatography (80 mm id column, silica gel, 8/92 EtOAc/hexane) to afford 7.17 g (80%) of a 0.39/0.61 cis to trans mixture of methyl 4-phenylbut-2-enoate. Trans isomer ^1H NMR ($CDCl_3$) δ 7.4-7.05 (m, 6 H), 5.81 (dt, J= 1.5, 15.5 Hz, 1H), 3.69 (s, 3 H), 3.55-3.47 (m, 2 H); Cis isomer ^1H NMR ($CDCl_3$) δ 7.4-7.13 (m, 5 H), 6.48 (d, J= 15.9 Hz, 1 H), 6.29 (dt, J= 7.0, 15.9 Hz, 1 H), 3.69 (s, 3 H), 3.28-3.20 (m, 2 H); Trans and Cis isomers ^{13}C NMR ($CDCl_3$) δ 171.9, 166.8, 147.6, 137.6, 136.8, 133.5, 128.8, 128.7, 128.5, 127.5, 126.7, 126.3, 121.9, 121.6, 51.9, 51.4, 38.4, 38.2.

A solution of benzylamine (2.14 g, 20 mmol) and cis and trans (39/61) methyl 4-phenylbut-2-enoate (3.52 g, 20.0 mmol) in 50 mL of MeOH was stirred for 11 days at RT. The reaction was then concentrated and purified by flash chromatography (60 mm column, silica gel, 4/6 EtOAc/hexane) to afford 2.00 g (35%) of methyl N-benzyl-3-amino-4-phenylbutanoate as an oil: ^1H NMR ($CDCl_3$) δ 7.35 (m, 10 H), 3.80 (s, 2 H, NCH_2), 3.63 (s, 3 H, CO_2CH_3), 3.35-3.22 (m, 1H), 2.87 (dd, J= 6.4, 13.5 Hz, 1 H), 2.74 (dd, J= 7.0, 13.5 Hz, 1 H), 2.42 (d, J= 6.4 Hz, 1 H), 1.63 (br s, 1 H, NH).

To a solution of the above amine (1.80 g, 6.35 mmol) in 50 mL of MeOH was added 0.18 g of 20% $Pd(OH)_2/C$. The reaction mixture was then treated with 50 psi of hydrogen in a Parr Type Shaker

for 36 h. The reaction mixture was filtered through celite and the filtrate concentrated to afford 1.18 g (96%) of methyl 3-amino-4-phenylbutanoate as a cloudy oil: ^{1}H NMR ($CDCl_3$) δ 7.38-7.17 (m, 5 H), 3.68 (s, 3 H, CO_2CH_3), 3.55-3.42 (m, 1 H), 2.76 (dd, J= 5.7, 13.3 Hz, 1 H), 2.61 (dd, J= 8.1, 13.3 Hz, 1 H), 2.50 (dd, J= 4.1, 15.9 Hz, 1 H), 2.32 (dd, J= 8.8, 15.9 Hz, 1 H), 1.46 (br s, 2 H);^{13}C NMR ($CDCl_3$) δ 172.9, 138.5, 129.3, 128.6, 126.5, 51.6, 49.6, 44.0, 41.7.

To a stirred solution of methyl 3-amino-4-phenylbutanoate (1.16 g, 6.00 mmol) in 25 mL of EtOAc was added 4-cyanophenyl isocyanate (0.858 g, 5.95 mmol). Solid began forming in the reaction mixture after 30 minutes. After stirring for 16 h, the reaction slurry was filtered to afford 0.858 g (43%) of the urea as a white powder. The filtrate was concentrated and residue slurried in ether. This slurry was filtered to afford an additional 0.770 g (38%) of N-(4-cyanophenyl)-N'-[3-(methyl 4-phenylbutanoate)]urea as a very pale yellow solid: mp 142-143.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.03 (s, 1H, NH), 7.64 (d, J= 8.8 Hz, 2 H), 7.53 (d, J= 8.8 Hz, 2 H), 7.35-7.15 (m, 5 H), 6.42 (d, J= 8.5 Hz, 1 H), 4.29-4.13 (m, 1 H), 3.58 (s, 3 H, CO_2CH_3), 2.9-2.73 (m, 2 H), 2.6-2.41 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 171.4, 153.9, 144.8, 138.2, 133.1, 129.1, 128.3, 126.3, 119.4, 117.4, 102.4, 51.4, 48.0, 39.9; IR (KBR) cm^{-1} 3340, 3320, 2220, 1740, 1673, 1596, 1537, 1508, 1322, 1239, 1175. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.67; N, 12.46. Found: C, 67.56; H, 5.73; N, 12.39.

To a stirred suspension of N-(4-cyanophenyl)-N'-[3-(methyl 4-phenylbutanoate)]urea (1.52 g, 4.51 mmol) in 65 mL of a 4.5/2 mixture of methanol/water was added 4.51 mL of 1 N NaOH. After stirring at RT for 19 h, the reaction mixture was heated to reflux for 3.5 h. The reaction mixture was concentrated and the residue slurried in CH_3CN/H_2O (50 mL/5 mL). The resultant slurry was filtered. The solid was dried in vacuo to afford 1.19 g (76%) of the desired urea as a white powder: ^{1}H NMR (DMSO-d_6) δ 11.12 (br s, 1 H), 8.20 (br s, 1 H), 7.9-7.45 (m, 4 H), 7.4-7.1 (m, 5

H), 4.1-3.9 (m, 1 H), 2.95 (dd, J= 5.9, 12.7 Hz, 1 H), 2.72 (dd, J= 8.2, 12.7 Hz, 1 H), 2.2-2.0 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 175.5, 154.7, 146.3, 139.9, 132.7, 129.2, 127.9, 125.6, 119.8, 117.3, 100.8, 49.4, 40.6; IR (KBR) cm^{-1} 3440, 2226, 1687, 1592, 1573, 1536, 1511, 1410, 1320, 1242, 1175. Anal. Calcd for $C_{19}H_{19}N_3O_3$-(1.05 H_2O): C, 59.33; H, 5.01; N, 11.53. Found: C, 59.30; H, 4.93; N, 11.50.

EXAMPLE 37

Preparation of N-(4-Cyanophenyl)-N'-[3-(5-phenylpentanoic acid)]urea sodium salt

A stirred suspension of 3-phenylpropionaldehyde (6.71 g, 50.0 mmol) and methyl (triphenylphosphoranylidene)-acetate (25.1 g, 75.0 mmol) in 150 mL of acetonitrile was refluxed for 1 h. The cooled reaction mixture was concentrated. The residue was slurried in 1/9 EtOAc/hexane (100 mL), and filtered. The filtrate was concentrated and purified by flash chromatography (1/9 EtOAc/hexane, silica gel) to afford 8.41 g (88%) of methyl 5-phenylpent-2-enoate as an oil: ^1H NMR ($CDCl_3$) δ 7.35-7.13 (m, 5 H), 7.00 (dt, 1 H, J= 6.8, 15.7 Hz), 5.84 (dt, 1 H, J= 1.5, 15.7 Hz), 3.70 (s, 3 H), 2.76 (t, 2 H, J= 7.5 Hz), 2.58-2.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.9, 148.3, 140.6, 128.4, 128.2, 126.1, 121.3, 51.3, 34.2, 33.8.

A solution of methyl trans-5-phenylpent-2-enoate (5.71 g, 30.0 mmol) and benzylamine (3.28 mL, 30.0 mmol) in 80 mL of methanol was stirred for 51 h. The reaction solution was concentrated and the residue purified to afford 2.64 g (46%) of starting olefin and 4.56 g (51%) of methyl N-benzyl-3-amino-5-phenylpentanoate as a clear oil: ^1H NMR ($CDCl_3$) δ 7.4-7.13 (m, 10 H), 3.78 (overlapping dd, 2 H, NCH2), 3.66 (s, 3 H, CO_2CH_3), 3.06 (m, 1 H), 2.68 (m, 2 H), 2.51 (d, 2 H, J= 6.1 Hz), 1.9-1.7 (m, 2 H), 1.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 142.0, 140.4, 128.3, 128.1, 126.9, 125.9, 53.7, 51.5, 50.8, 38.8,

36.1, 32.0. IR (KBr) cm^{-1} 3080, 3040, 2950. 2860, 1730, 1500, 1460, 1440. Anal. Calcd for $C_{19}H_{23}N_1O_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 77.11; H, 7.93; N, 4.75.

To a solution of methyl N-benzyl-3-amino-5-phenylpentanoate in 50 mL of methanol was added 100 mg of 20% $Pd(OH)_2$. This suspension was treated with 50 psi of hydrogen in a Parr Type Shaker. After 15 h and 39 h, 100 mg of 20% $Pd(OH)_2$ was added. After 63 h, the reaction mixture was filtered through celite to remove the catalyst and the filtrate concentrated to afford 2.71 g (97%) of methyl 3-amino-5-phenylpentanoate as a clear oil: ^1H NMR ($CDCl_3$) δ 7.35-7.14 (m, 5 h, Ph), 3.68 (s, 3 H, CO_2CH_3), 3.28-3.15 (m, 1 H, CHN), 2.82-2.48 (m, 2H, CH_2Ar), 2.50 (dd, 1 H, J = 4 Hz, 15.7 Hz), 2.31 (dd, 1 H, J= 8.8 Hz, 15.7 Hz), 1.78-1.6 (m, 2 H), 1.47 (s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 172.8, 141.6, 128.4, 128.3, 125.8, 51.5, 47.9, 42.5, 39.5, 32.4; IR (KBr) cm^{-1} 3390, 3300, 3040, 2960, 2940, 2860, 1730, 1660, 1500, 1454, 1437. Anal. Calcd for $C_{12}H_{17}N_1O_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.98; H, 8.08; N, 6.30.

To a stirred solution of methyl 3-amino-5-phenylpentanoate (2.07 g, 9.99 mmol) in 35 mL of ethyl acetate was added 4-cyanophenyl isocyanate (1.44 g, 9.99 mmol). After 24 h, the reaction mixture was concentrated. The residue was slurried in 50 mL of ether and the slurry was filtered to afford after drying 3.01 g (86%) of the urea as an off-white powder: ^1H NMR (DMSO-d_6) δ 9.0 (s, 1 H), 7.65 (d, 2 H, J = 8.8 Hz), 7.57 (d, 2 H, J= 8.8 Hz), 7.22 (m, 5 H, Ph), 6.47 (d, 1 H, J= 8.7 Hz, NH), 4.0 (m, 1 H), 3.57 (s, 3 H, CH_3), 2.7-2.5 (m, 4 H), 1.77 (m, 2 H) contaminated with ethyl acetate; IR(KBr) cm^{-1} 3340, 2240, 1730, 1680, 1600, 1550, 1520, 1320, 1240.

To a stirred suspension of the above urea (2.50 g, 7.11 mmol) in a mixture of 150 mL of methanol and 30 mL of water was added 28 mL of 1 N NaOH. The progress of the reaction was monitored by HPLC. After 44 h, the reaction mixture was partially concentrated

to remove the methanol and the residue slurried in 100 mL of water. The resulting slurry was filtered to afford after drying in vacuo, 2.11 g (83%) of the product as a white solid: ^1H NMR ($DMSO-d_6$) δ 10.93 (br s, 1 H), 7.95 (br s, 1 H), 7.73 (d, 2 H, J = 8.4 Hz), 7.54 (d, 2 H, J= 8.4 Hz), 7.14 (m, 5 H), 3.9 (m, 1 H), 2.56 (m, 2 H), 2.23 (d, 2 H, J= 4.4 Hz), 1.7 (m, 2 H); IR(KBr) cm^{-1} 3420, 3160, 3080, 3020, 2920, 2228, 1698, 1690, 1594, 1572, 1542, 15412, 1408, 1320, 1240, 1176. Anal. Calcd for $C_{19}H_{18}N_3O_3Na$-(1.32 H_2O): C, 59.56; H, 5.43; N, 10.97. Found: C, 59.26; H, 5.10; N, 11.10.

EXAMPLE 38

Preparation of N-(4-Cyanophenyl)-N′-[3-(3-(4′-nitrophenyl)propionic acid)]urea sodium salt

A stirred suspension of ammonium acetate (30.8 g, 400 mmol) and 4-nitrobenzaldehyde (30.2 g, 200 mmol) in 50 mL of 95% ethanol was heated to 45 °C. To the resulting thick slurry was added 75 mL of 95% ethanol and malonic acid (20.8 g, 200 mmol). The reaction mixture was heated at reflux for 24 h. The cooled reaction mixture was filtered and the solid washed with copious amounts of ethanol. The solid was air-dried to afford 42.55 g of crude product as a pale orange powder. The crude product (35 g) was slurried in 300 mL of water, heated to 55 °C, and the pH adjusted to 1 with concentrated HCl. After cooling to RT, the slurry was filtered and the solid washed with water. The filtrate was concentrated to approximately 250 mL and the pH adjusted to 7 with 1 N NaOH. The resulting suspension was stirred overnight and then filtered. The solid was dried in vacuo to afford 4.95 g (14%) of 3-amino-3-(4′-nitrophenyl)propionic acid as a white powder: ^1H NMR (D_2O/NaOD/TSP) δ 8.15 (d, J = 8.7 Hz, 2 H), 7.56 (d, J = 8.7 Hz, 2 H), 4.38 (t, J = 7.3 Hz, 1 H), 2.72-2.52 (m, 2 H); ^{13}C NMR (D_2O/NaOD/TSP) δ 182.2, 155.3, 149.3, 130.1, 126.6, 55.5, 49.5.

To a stirred suspension of 4-cyanophenyl isocyanate (2.74 g, 19.0 mmol) in 100 mL of CH_3CN was added a solution of 3-amino-3-(4'-nitrophenyl)propionic acid (4.00 g, 19.0 mmol) and NaOH (0.76 g, 19 mmol) in 30 mL of water. The reaction suspension became homogeneous after the addition was complete. The reaction mixture was stirred for 6 h, then partially concentrated to remove the CH_3CN. A small amount of solid which had formed was removed by filtration. The filtrate was concentrated to a thick oil and then diluted with 50 mL of EtOH. The resulting slurry was filtered and the solid washed with EtOH. The solid was dried in vacuo to afford 2.98 g (42%) of the urea as an off-white powder: ^1H NMR (D_2O/TSP) δ 8.04 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.17 (t, J = 6.9 Hz, 1 H), 2.85-2.65 (m, 2 H); ^{13}C NMR (D_2O/TSP) δ 181.2, 158.6, 153.4, 149.3, 146.2, 136.2, 129.9, 126.7, 122.9, 121.4, 106.4, 54.7, 46.7; IR(KBr) cm^{-1} 3320, 2227, 1700, 1600, 1580, 1540, 1520, 1400, 1350, 1320, 1236, 1180. Anal. Calcd for $C_{17}H_{13}N_4O_5Na$-(1.13 H_2O): C, 51.45; H, 3.88; N, 14.12. Found: C, 51.32; H, 3.68; N, 13.98.

EXAMPLE 39

Preparation of (S)-N-(4-Cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]

To a stirred solution of 3-pyridinecarboxaldehyde (21.4 g, 0.20 mol) in benzene (250 mL) was added (S)-1-phenylethylamine (24.2 g, 0.20 mol). The reaction mixture was refluxed for 2 h with a Dean-Stark trap. The reaction mixture was then allowed to cool to room temperature and concentrated. Purification of the residue by distillation afforded 40.8g (97 %) of N-[(S)-1-phenyethyl)]pyridine-3-carboxaldimine (1): B.p. 123 °C/0.25 Torr; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, J = 6.6 Hz, 3H), 4.55 (q, J = 6.6 Hz, 1H), 7.21-7.43 (m, 6H), 8.14 (d, J = 7.9 Hz, 1H), 8.37 (s, 1H), 8.62 (d, J = 3.4 Hz, 1H), 8.7 (s, 1H). ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ 156.3, 151.3, 150.2, 144.6, 134.5, 131.7, 125.4, 126.9, 126.4, 123.4, 69.9, 24.7.

A stirred suspension of 32.7 g (5 equiv) of activated zinc dust in 300 mL of THF was heated to reflux under N_2. Several 0.1mL portions of methyl bromoacetate were added with vigorous stirring to initiate the reaction. When a green color appeared, 21.0 g (0.100 mol) of N-[(S)-1-phenyethyl)]pyridine-3-carboxaldimine in 100 mL of THF was added. Then 37.9 mL (4 equiv) of methyl bromoacetate was added dropwise over 45 min to the refluxing mixture. The mixture was refluxed for an additional 10 min, cooled to room temperature, diluted with 500 mL of THF, and the reaction quenched with 140 mL of 50% aqueous K_2CO_3. Rapid stirring for 45 min gave a suspension. The THF layer was decanted, and the residue was rinsed with THF. The combined THF layers were concentrated and the resulting crude oil dissolved in ethyl acetate. The reaction mixture was then washed with water and brine, dried ($MgSO_4$) and concentrated to afford 23.2 g (92 %) of a mixture of diastereomers (1:1) of the β-lactam (4S) and (4R)[(S)-N-phenyethyl]-3-amino-3-(3-pyridyl)propionate and β-(phenylethylamine)-(3-pyridyl)methylpropionate.

The product obtained from the above reaction was dissolved in 200 mL of 6N HCl. The reaction mixture was refluxed for 15 min, cooled to room temperature, partially concentrated and the pH adjusted to 4-5 with basic resin. The reaction mixture was filtered, and concentrated. The residue was dissolved in methanol, dried over $MgSO_4$, filtered and concentrated to afford an oil consisting of a mixture of the diastereomers, N-(S)-phenyethyl-3-(R,S)-amino-3-(3-pyridyl)propionic acid.

To the residue (24.8 g) obtained by the above procedure was added 19.8 g (0.24 mol) of benzyl alcohol in 200 mL of methylene chloride and 1.0 g of DMAP. The reaction mixture was cooled to 0 °C and 37.7 g (0.18 mol) of DCC in 100 mL of methylene chloride was added. The mixture was allowed to warm to room temperature

and stirred an additional 12 h. The reaction mixture was then filtered to remove the DCU and washed with water, brine, and dried ($MgSO_4$). After silica chromatography (elution with 1:1 hexane-ethyl acetate), 3.91 g (12%) of benzyl N-[(S)-phenyethyl]-3-(S)-amino-3-(3-pyridyl)propionate was isolated from the mixture of diastereomers as an oil. R_f = 0.32 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.7 Hz, 3H), 2.20 (bs, 1H), 2.65 (ddd, J = 15.4, 9.0, 5.1 Hz, 2H), 3.40 (q, J = 6.7 Hz, 1H), 3.80 (dd, J = 8.9, 5.1 Hz, 1H), 5.10 (dd, J = 27.0, 12.2 Hz, 2H), 7.10 (d, J = 6.4 Hz, 2H), 7.23-7.47 (m, 9H), 7.56 (d, J = 7.8 Hz, 1H), 8.40 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 149.2, 149.0, 144.5, 137.7, 135.5, 134.7, 128.5, 125.3, 127.0, 126.5, 123.5, 66.4, 55.0, 54.2, 42.9, 24.9.

To a stirred suspension of 3.0 g of the same amino ester and an equal weight of 10% Pd/C in dry methanol (50 mL), was added anhydrous ammonium formate (5.2 g, 83 mmol) in a single portion under nitrogen. The resulting reaction mixture was stirred at reflux for 6 h and then the catalyst was removed by filtration through a celite pad. The reaction mixture was concentrated and refluxed in methanol (30 mL) while 30 mL of ethyl acetate was slowly added over 15 min. The slurry was allowed to cool to room temperature, and filtered to afford 457 mg of the β-amino acid, (S)-3-amino-3-(3-pyridyl)propionic acid. The residue from the filtrate was resubmitted to the above conditions to yield another 210 mg of the β-amino acid, (S)-3-amino-3-(3-pyridyl)propionic acid. The total yield was 667 mg (48%) of the amino acid. ^1H NMR (300 MHz, D_2O) δ 2.98 (dq, J = 18.2, 6.9 Hz, 2H), 4.73 (t, J = 7.3 Hz, 1H), 7.52 (dd, J = 17.5, 5.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 20 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.6, 149.5, 147.7, 136.3, 132.6, 124.9, 50.5, 40.0.

To a solution of sodium hydroxide (120 mg, 3 mmol) and 498 mg (3.4 mmol) of (S)-3-amino-3-(3-pyridyl)propionic acid in methanol

(45 mL) was rapidly added a solution of p-cyanophenyl isocyanate in methyl acetate (65 mL). The temperature of the reaction mixture dropped 2-5 °C after the addition. The reaction mixture was then stirred for 15 min and concentrated. The residue was dissolved in methanol (5 mL) and ethyl acetate (5 mL) and refluxed until the solution becomes turbid (2-5 min). To this mixture was added ethyl acetate (45 mL) slowly, and the heating was stopped halfway through the addition. The mixture was allowed to cool slowly to 45 °C, at which time the solid was filtered off. The solid was washed with ethyl acetate (2 X 2.5 mL) and dried to afford 900 mg (90%) of the product as a white solid. $[\alpha]^{26}$ = 59.5° (c 5.12, H_2O). ^1H NMR (300 MHz, D_2O) δ 2.69 (dd, J = 7.2, 1.8 Hz, 2H), 5.09 (t, J = 6.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.39 (dd, J = 7.9, 4.9 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.81 (dt, J = 8.0, 1.5 Hz, 1H), 8.36 (dd, J = 4.9, 1.2 Hz, 1H), 8.49 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75.5 MHz, D_2O) δ 178.5, 156.0, 147.6, 146.8, 143.3, 138.6, 135.2, 133.4, 124.3, 120.1, 118.8, 103.8, 50.2, 43.8. Anal. Calcd for $C_{16}H_{13}N_4NaO_3$-$6H_2O$ (343.10) δ C 56.01, H 4.17, N 16.03; found: C 56.10 , H 4.08, N 16.14.

EXAMPLE 40

Conversion of (S)-N-(4-Cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea to (S)-N-(4-Carbamoylphenyl)-N'-[3-(3-(3-pyridyl) propionic acid urea sodium salt

Hydrogen peroxide (30%, 0.3 mL, 2.64 mmol) was added to a stirred suspension of (S)-N-(4-Cyanophenyl)-N'-[3-(3-(3-pyridyl)propionic acid)]urea (0.250 g, 0.753 mmol) in ethanol (1 mL), water (1 mL) and sodium hydroxide (6N, 0.2 mL, 1.20 mmol). The reaction mixture was stirred for 25 min at room temperature until the contents of the flask became clear and the evolution of gas (oxygen) stopped. Sodium bisulfite (0.2 g) was added to the reaction mixture to destroy excess hydrogen peroxide. The reaction mixture was

concentrated in vacuo at room temperature and then chromatrographed (PRP-1 column HPLC, 2% acetonitrile in water as the eluant). Pure fractions were combined and lyophilized to afford 0.20 g (76%) of the desired product as a white crystalline powder. ^{1}H NMR (D_2O) d 2.72 (d, 2H, J=7.0 Hz), 5.13 (t, 1H, J=7.0 Hz), 7.37 and 7.73 (AB quartet, 4H, J=7.1 Hz), 7.42-7.48 (m, 1H), 7.88 (d, 1H, J=7.7 Hz), 8.43 (m 1H), 8.53 (m, 1H).

EXAMPLE 41

Preparation of (S)-N-(4-Cyanophenyl)-N'-[3-(3-phenylpropionic acid)]urea

(S)-3-amino-3-phenylpropionic acid hydrochloride was separated from commercially available 3-amino-3-phenylpropionic acid hydrochloride (Aldrich) by the method of Fisher, Scheibler, and Groh as it appears in "Chem. Ber.", Vol. 43 pages 2020-3- (1910). The compound, 1.08 grams, was a single peak by HPLC (chiral); $[\alpha]D_{20}$ + 2.36, 3.0% in MeOH; lit. $[\alpha]24D$ + 3.3o, 2.95% in MeOH. Anal. Calcd for $C_9H_{11}NO_2$-HCl$(H_2O)_{0.11}$: C, 53.08; H, 6.05; N, 6.88. Found: C, 53.06; H,6.04; N, 6.82.

To a stirred suspension of (S)-3-amino-3-phenylpropionic acid hydrochloride (1.00 g, 6.05 mmol) and 4-cyanophenyl isocyanate (1.0 g, 6.9 mmol) in 50 mL of acetonitrile was added 13 mmol of 1 N NaOH. The clear solution which immediately formed was stirred overnight before the solvents were removed at reduced pressure. The residue was dissolved in 100 mL of water and washed with ethyl acetate (2 x 50 mL). The aqueous layer was acidified to a pH of 2 with concentrated HCl to produce a gummy solid. The gum yielded, after thorough drying in a vacuum oven, 1.20 grams (64%) of the desired product, as a brittle white solid. The product showed one peak on HPLC using a Daicel Chiral pak WH column; IR (KBr) cm^{-1} 3360, 2220, 1710, 1670, 1590, 1540, 1410, 1320, 1240, 1180; 1H NMR (DMSO-d_6) d 9.2 (s, 1H), 7.7 (d, 2H, J=8.7Hz), 7.6 (d, 2H, J=8.7Hz), 7.3 (m, 5H), 7.1 (d, 1H, J=8.7Hz), 5.2 (q, 1H),

2,8 (m, 2H); [α]D_{21}-3.45°, 5.0% in MeOH. Anal. Calcd for $C_{17}H_{15}N_3O_3\cdot(H2O)_{0.5}$: C, 64.29; H, 5.05; N, 13.23. Found C, 64.28; H, 5.08; N, 12.96.

EXAMPLE 42

Preparation of
N-[5-(2-Cyanopyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea
Sodium salt

A solution of 2-cyano-5-pyridylcarbonylazide (4.05 g, 23.3 mmol) in 100 mL of dried toluene was heated at 80°C for three hours. To this cooled solution was added 4.23 g (22.4 mmol) of 3-amino-3-phenylpropionic acid sodium salt and the slurry stired overnight at room temperature. The solvent was removed at reduced pressure and the residue chromatographed using a water mobile phase on a PRP-1 preparative column. The desired fractions were combined and lyophilized to give 1.4 grams (18%) of a white fluffy powder: IR (KBr) cm^{-1} 3400, 2230, 1700, 1580, 1560, 1400, 1240; ^1H NMR (D_2O) δ 8.5 (m, 3H), 7.9 (m, 2H), 7.7 (d, 1H, J=8.7Hz), 7.45 (m, $_1H$), 5.2 (m, 1H), 2.8 (m, 2H): ^{13}C NMR (D_2O) δ 181.2, 158.5, 150.5, 149.6, 143.9, 142.6, 141.2, 138.0, 132.8, 128.6, 127.1, 127.0, 120.4, 53.1, 46.5.

EXAMPLE 43

Preparation of N-[5-(2-Cyanopyridyl)]-N'-[3-(3-phenylpropionic acid)]urea

To a solution of 3-amino-3-phenylpropionic acid (2.00 g, 12.0 mmol) in 24 mL 0.5 N NaOH was added a solution of 2-cyano-5-pyridyl isocyanate (2.03 g, 13.9 mmol) in 20 mL of acetonitrile:acetone. The reaction mixture was stirred overnight and then the solvents removed at reduced pressure on a RotoVac. The residue ws dissolved in 150 of equal parts of water and dichloromethane. The aqueous layer was extraced with

dichloromethane (2 x 50 mL) and acidified to a pH of 2-3 with dilute HCl. The gummy precipitate was stirred overnight and the desired product isolated by filtration to yield 1.4 g (37%) of a white powder: mp 103-107°C; IR (KBr) cm^{-1} 3350, 2233, 1700, 1680, 1540, 1235; ^{1}H NMR (DMSO-d_6) δ 9.4 (s, 1H), 8.6 (m, 1H), 8.1 (m, 1H), 7.9 (m, 1H), 7.2-7.4 (m, 6H), 5.2 (q, 1H), 2.8 (m, 2H); ^{13}C NMR (DMSO-d6) δ 172.3, 154.3, 143.5, 142.3, 142.0, 131.2, 130.1, 128.9, 127.9, 125.4, 119.6, 53.2, 51.8.

EXAMPLE 44

Preparation of N-(6-Indazolyl)-N'-[3-(3-phenylpropionic acid)urea)]

To a stirred solution of 1,1'-carbonyldiimidazole (1.82 g, 11.2 mmol) and imidazole (1.14 g, 16.8 mmol) in 30 mL of THF at RT was added a solution of methyl 3-phenylpropionate (2.00 g, 11.2 mmol) in 10 mL of THF over 20 minutes. Then, a suspension of 6-aminoindazole (1.49 g, 11.2 mmol) in 20 mL of THF was rapidly added. After 1 h, the reaction mixture was refluxed for 16 h. The reaction mixture was then concentrated. The residue was purified by flash chromatography (silica gel, 4/96 methanol/dichloromethane) to yield a slightly impure sample of N-(6-indazolyl)-N'-[3-(methyl 3-phenylpropionate)]urea. This sample was purified by flash chromatography (silica gel, 16/84 ethyl acetate/dichloromethane) to afford 0.86 g (23%) of the desired ester which was used in the next reaction.

To a stirred solution of N-(6-Indazolyl)-N'-[3-(methyl 3-phenylpropionate)]urea(0.800 g, 2.36 mmol) in 8 mL of methanol was added 2.36 mL of 1 N NaOH(aq). After 71 h, the reaction solution was partially concentrated to remove the methanol and diluted to a volume of 25 mL with water. The resulting slurry was washed with ethyl acetate (2 x 25 mL ea.). The aqueous layer was partially concentrated to remove traces of ethyl acetate and then acidified with 3.0 mL of 1 N HCl followed by the addition of 0.5

g of NaOH. A gum formed which solidified on stirring. The slurry was filtered and the solid dried to afford 0.56 g (73%) of the urea: ^{1}H NMR (DMSO-d_6) δ 12.35 (br s, 1 H), 8.68 (d, 1 H, J= 8.9 Hz), 2.68 (dd, 1 H); ^{13}C NMR (DMSO-d_6) δ 172.1, 151.9, 150.4, 142.4, 141.1, 137.7, 128.3, 121.5, 116.6, 113.4, 95.3, 50.4.

EXAMPLE 45

N-[5-(2-Carbamoylpyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea Sodium Salt

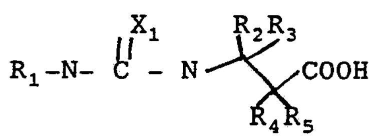
To a stirred solution of N-[5-(2-cyanopyridyl)]-N'-[3-(3-(3-pyridyl)propionic acid)]urea sodium salt (108 mg, 0.32 mmol) in 3 mL of 1:1 ethanol/water were added 0.1 mL of 6 N NaOH (0.6 mmol) and 0.15 mL of 30% hydrogen peroxide. The reaction was stirred for thirty minutes at room temperature at which time 0.3 g of sodium bisulfite was added to quench the reaction. The solvents were removed at reduced pressure and the residue chromatographed on a PRP-1 preparative chromatography column. The desired fractions were combined and lyophilized to give 30 mg of the desired urea as a white solid; IR (KBr) cm^{-1} 3400, 1680, 1580, 1550, 1400, 1240: ^{1}H NMR (D_2O) δ 8.4 (s, 1H), 8.3 (s, 2H), 7.8-7.6 (m, 3H), 7.3 (m, 1H), 5.6 (t, 1H, J=7.3Hz), 2.6 (d, 2H, J=7.3Hz); ^{13}C NMR (D_2O) δ 182.2, 173.0, 159.8, 151.3, 150.5, 145.9, 143.2, 142.7, 142.3, 139.0, 130.2, 128.1, 127.1, 54.0, 47.6.

EXAMPLE 46

N-[5-(2-Carbamoylpyridyl)]-N'-[3-(3-phenylpropionic acid)]urea Sodium Salt

To a stirred suspension of N-[5-(2-cyanopyridyl)]-N'-[methyl 3-(3-phenylpropionate)]urea (108. mg, 0.33 mmol) in 3 mL of 1:1 ethanol/water were added 0.15 mL of 6 N NaOH (0.90 mmol) and 0.15 mL of 30% hydrogen peroxide. The reaction was stirred for 30

minutes at room temperature at which time 0.3 g of sodium bisulfite was added to quench the reaction. The solvents were removed at reduced presssure and the residue chromatographed on a PRP-1 preparative chromatography column. The desired fractions were combined and lyophilized to give 90 mg (78%) of the desire urea as a fluffy white powder; IR (KBr) cm^{-1} 3320, 1680, 1580, 1560, 1560, 1410, 1240: ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H), 9.25 (s, 1H), 8.75 (s, 1H), 8.1 (d, 1H, J=9Hz), 7.9 (s, 1H), 7.8 (d, 1H, J=9Hz), 7.4-7.1 (m, 6H), 5.1 (m, 1H), 2.4 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 175.5, 166.4, 155.2, 146.1, 141.7, 141.1, 137.9, 128.0, 126.1, 123.6, 122.1, 52.24, 46.0.

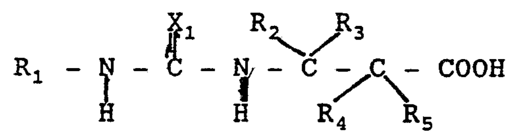


	R_1	X_1	R_2	R_3	R_4	R_5
Ex. 1	4-Ethoxycarbonylphenyl	O	3-Phenyl	H	H	H
Ex. 2	4-Acetylphenyl	O	3-Phenyl	H	H	H
Ex. 3	4-Bromophenyl	O	3-Phenyl	H	H	H
Ex. 4	4-Cyanophenyl	O	3-Phenyl	H	H	H
Ex. 5	4-Cyanophenyl	O	3-Pyridyl	H	H	H
Ex. 6	4-Nitrophenyl	O	3-Phenyl	H	H	H
Ex. 7	4-Carbomoylphenyl	O	3-Phenyl	H	H	H
Ex. 8	4-Sulfamylphenyl	O	3-Phenyl	H	H	H
Ex. 9	4-Carbomethoxylphenyl	O	3-Phenyl	H	H	H
Ex. 10	4-Carboethoxyphenyl	O	3-Pyridyl	H	H	H
Ex. 11	4-Carbamoylphenyl	O	3-Pyridyl	H	H	H
Ex. 12	4-Carboxyphenyl	O	3-Pyridyl	H	H	H
Ex. 13	4-Iodophenyl	O	3-Phenyl	H	H	H
Ex. 14	4-Chlororphenyl	O	3-Phenyl	H	H	H
Ex. 15	3-Chlorophenyl	O	3-Phenyl	H	H	H
Ex. 16	4-Methylphenyl	O	3-Phenyl	H	H	H
Ex. 17	4-Trifluorophenyl	O	3-Phenyl	H	H	H
Ex. 18	4-Cyanophenyl	O	4-Methoxyphenyl	H	H	H
Ex. 19	4-Cyanophenyl	O	2-Naphthyl	H	H	H

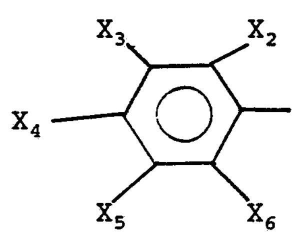
Ex. 20	4-Cyanophenyl	O	3,4-Dimethoxy-phenyl	H	H	H
Ex. 21	4-Cyanophenyl	O	3,4-Methylene-dioxyphenyl	H	H	H
Ex. 22	4-Cyanophenyl	O	1-cyclooctyl	H	H	H
Ex. 23	4-Cyanophenyl	S	3-Phenyl	H	H	H
Ex. 24	4-Cyanophenyl	O	3-Quinolyl	H	H	H
Ex. 25	4-Methoxycarbonylphenyl	S	3-Phenyl	H	H	H
Ex. 26	4-Cyanophenyl	O	3-Cyclohexyl ethyl	H	H	H
Ex. 27	4-Cyanophenyl	O	3-Nitrophenyl	H	H	H
Ex. 28	4-Cyanophenyl	O	4-Pyridyl	H	H	H
Ex. 29	4-Carboxyphenyl	O	3-Phenyl	H	H	H
Ex. 30	Phenyl	O	3-Phenyl	H	H	H
Ex. 31	4-Formylphenyl	O	3-Phenyl	H	H	H
Ex. 32	4-Hydroxyphenyl	O	3-Phenyl	H	H	H
Ex. 33	4-Cyanophenyl	O	3'-Hydroxy-4'-methoxyphenyl	H	H	H
Ex. 34	4-Cyanophenyl	O	Hexyl	H	H	H
Ex. 35	4-Formylphenyl	O	3-Pyridyl	H	H	H
Ex. 36	4-Cyanophenyl	O	Benzyl	H	H	H
Ex. 37	4-Cyanophenyl	O	Phenyethyl	H	H	H
Ex. 38	4-Cyanophenyl	O	4-Nitrophenyl	H	H	H
Ex. 39	4-Cyanophenyl	O	(S)-3 Pyridyl	H	H	H
Ex. 40	4-Carbamoyl	O	(S)-3 Pyridyl	H	H	H
Ex. 41	4-Cyanophenyl	O	(S)-3-Phenyl	H	H	H
Ex. 42	5-(2-Cyanopyridyl)	O	3-Pyridyl	H	H	H
Ex. 43	5-(2-Cyanopyridyl)	O	3-Phenyl	H	H	H
Ex. 44	6-Indazolyl	O	3-Phenyl	H	H	H
Ex. 45	5-(2-Carbamoylpyridyl)	O	3-Phenyl	H	H	H
Ex. 46	5-(2-Carbamoylpyridyl)	O	3-Phenyl	H	H	H

WE CLAIM:

1. A compound corresponding to the formula



wherein X_1 is O or S, wherein R_1 is an optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, said phenyl corresponding to



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are selected from the group consisting of:

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
$CH=NOCH_3$,
$CH=NOH$,
CHO,
CH_2OCH_3,
CH_2OH,
CN,
$COCF_3$,
COC_1-C_3 alkyl,

$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,
$COOC_1$-C_3 alkyl,
COOH,
NH_2,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
NHCHO,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
$NHCOCH_3$,
$NHCONH_2$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 may not be OCH_2CH_3
$OCOCH_3$,
OH,
SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2NC(C_1$-C_3 alkyl$)_2$,
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring,

wherein R_2, R_3, R_4, and R_5 are the same or different and are selected from the group consisting of

H,
optionally substituted straight chain or branched

C_1-C_{10} alkyl,
optionally substituted cyclic C_3-C_{10} alkyl,
optionally substituted cyclic,
optionally substituted heterocyclic including optionally substituted heteroaromatics,
optionally substituted bicyclic including optionally substitute aromatic bicyclic, or
optionally substituted phenyl, and

enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining groups is not H.

2. The compound of claim 1 wherein R_1 is selected from the group consisting of optionally substituted phenyl, optionally substituted pyridyl, optionally substituted pyrimidyl, 2-indanyl, or 6-indazolyl.

3. The compound of claim 2 wherein R_1 is an optionally substituted phenyl wherein X_4 is selected from the group consisting of CN, NO_2, CO_2CH_3, $CONH_2$, HCO, SO_2NH_2, CH_3SO_2, and $CO_2C_2H_5$.

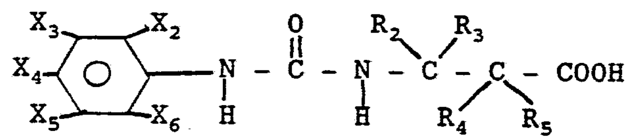
4. The compound of claim 2 wherein R_1 is an optionally substituted pyridyl.

5. The compound of claim 2 wherein R_1 is an optionally substituted pyrimidyl.

6. The compound of claim 1 wherein R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, quinolyl, or isoquinolyl.

7. The compound of claim 1 wherein X_1 is O.

8. The compound of claim 1 having the formula:



9. The compound of claim 8 wherein X_2, X_3, X_5 and X_6 are H and X_4 is selected from the group consisting of CN, NO_2, $CO_2C_2H_5$, CO_2CH_3, $CONH_2$, Cl, Br, F, I, HCO, CH_3CO, SO_2NH_2 and CH_3SO_2.

10. The compound of claim 8 wherein R_3, R_4 and R_5 are H and R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, naphthyl, quinolyl, and $(CH_2)_{1-6}$ cycloalkyl (C_3-C_8).

11. The compound of claim 9 wherein X_4 is selected from the group consisting of CN, NO_2, $CONH_2$, CHO, CO_2CH_3 and $CO_2C_2H_5$.

12. The compound of claim 11 wherein R_2 is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl.

13. The compound of claim 11 wherein X_2, X_3, X_5 and X_6 are H, X_4 is selected from the group consisting of CN, NO_2, $CONH_2$, HCO, $CO_2C_2H_5$, CO_2CH_3, Cl, Br, F, I, CH_3CO, CH_3SO_2, and SO_2NH_2, R_3, R_4 and R_5 are H, and R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, naphthyl, quinolyl and $(CH_2)_{1-6}$cycloalkyl (C_3-C_8).

14. The compound of claim 13 wherein X_4 is CN and R_2 is 3-pyridyl.

15. The compound of claim 13 wherein X_4 is CN and R_2 is phenyl.

16. The compound of claim 13 wherein X_4 is CN and R_2 is 4-pyridyl.

17. The compound of claim 13 wherein X_4 is NO_2 and R_2 is phenyl.

18. The compound of claim 13 wherein X_4 is $CO_2C_2H_5$ and R_2 is phenyl.

19. The compound of claim 13 wherein X_4 is CN and R_2 is CH_2-cyclohexyl.

20. The compound of claim 4 wherein R_3, R_4 and R_5 are H and R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, naphthyl, quinolyl, and $(CH_2)_{1-6}$ cycloalkyl (C_3-C_8).

21. The compound of claim 5 wherein R_3, R_4 and R_5 are H and R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, naphthyl, quinolyl, and $(CH_2)_{1-6}$ cycloalkyl (C_3-C_8).

22. The compound of claim 13 wherein X_4 is $CONH_2$ and R_2 is 3-pyridyl.

23. The compound of claim 13 wherein X_4 is CHO and R_2 is 3-pyridyl.

24. The compound of claim 13 wherein X_4 is $CONH_2$ and R_2 is phenyl.

25. The compound of claim 13 wherein X_4 is CHO and R_2 is phenyl.

26. The compound of claim 13 wherein X_4 is $CONH_2$ and R_2 is 4-pyridyl.

27. The compound of claim 13 wherein X_4 is CHO and R_2 is 4-pyridyl.

28. The compound of claim 20 wherein R_1 is 5-(2-cyanopyridyl) and R_2 is 3-pyridyl.

29. The compound of claim 20 wherein R_1 is 5-(2-cyanopyridyl) and R_2 is phenyl.

30. The compound of claim 1 wherein the compound is selected from the group of physiologically acceptable salts comprising hydrochloride, phosphate, citrate, sulfate, bisulfate, sodium, potassium, ammonium, calcium, malate, tosylate, benzoate and magnesium salts.

31. A process for sweetening edible products comprising foods, beverages, confections, chewing gums, pharmaceuticals, veterinary preparations and toilet, cosmetic and hygiene products characterized in that an effective sweetening amount of a compound of claim 1 is added to said edible products.

32. Edible products sweetened according to the process of claim 31.

33. Sweetening compositions characterized in that said compositions comprise an effective sweetening amount of a compound of claim 1 and a physiologically acceptable carrier therefor.

34. The sweetening compositions of claim 33 wherein the carrier is a bulking agent.

35. The sweetening compositions of claim 33 wherein the carrier is selected from the group consisting of water, polymeric dextrose, starch and modified starches, maltodextrins, cellulose, methylcellulose, cellobiitol, carboxymethylcellulose, maltitol, hydroxypropylcellulose, hemicelluloses, microcrystalline cellulose, other cellulose derivatives, sodium alginate, pectins and other gums,

lactose, maltose, glucose, leucine, glycerol, mannitol, sorbitol, sodium bicarbonate, and phosphoric, citric, tartaric, fumaric, benzoic, sorbic, and propionic acids and their sodium, potassium and calcium salts and mixtures of any of the above.

36. A sweetening composition comprising:

(a) a first sweetening agent comprising a compound of claim 1; and

(b) a second sweetening agent which is not a compound of claim 1.

37. The sweetening composition of claim 36 further comprising a bulking agent.

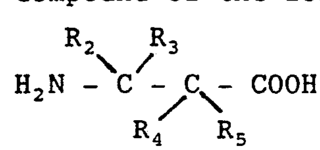
38. The sweetening composition of claim 36 wherein said second sweetening agent is selected from the group consisting of sucrose, corn syrups, fructose, aspartame, alitame, neohesperidin dihydrochalcone, high fructose corn syrup, hydrogenated isomaltulose, stevioside type sweeteners, L-sugars, lactitol, neosugar, glycyrrhizin, xylitol, acesulfam-K, sodium saccharin, potassium saccharin, calcium saccharin, cyclamic acid and the sodium, potassium, and calcium salts thereof, sucralose, monellin, thaumatin and mixtures thereof.

39. A process comprising

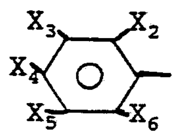
(a) reacting a compound of the formula:

$$R_1NCX_1$$

with a compound of the formula:



wherein X_1 is O or S, wherein R_1 is an optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, said phenyl corresponding to:



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are selected from the group consisting of:

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
$CH{=}NOCH_3$,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
CHO,
CH_2OCH_3,
CN,
$COCF_3$,
COC_1-C_3 alkyl,
$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,
$COOC_1$-C_3 alkyl,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
NHCHO,

$NHCOCH_3$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 may not be OCH_2CH_3
$OCOCH_3$,
SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2N(C_1$-C_3 alkyl$)_2$,
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring, and

wherein R_2, R_3, R_4, and R_5 are the same or different and are selected from the group consisting of
H,
optionally substituted straight chain or branched C_1-C_{10} alkyl,
optionally substituted cyclic C_3-C_{10} alkyl, optionally substituted cyclic,
optionally substituted heterocyclic including optionally substituted heteroaromatics, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, and enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining group is not H; and

(b) recovering the urea compound formed in step (a) above.

40. The process of claim 39 wherein R_1 is an optionally substituted phenyl, optionally substituted pyridyl, or optionally substituted pyrimidyl.

41. The process of claim 39 wherein R_1 is an optionally substituted phenyl wherein X_2, X_3, X_5 and X_6 are H, and X_4 is selected from the group consisting of CN, NO_2, $CO_2C_2H_5$, CO_2CH_3, $CONH_2$, Cl, Br, F, I, HCO, CH_3CO, SO_2NH_2 and CH_3SO_2, and X_1 is O.

42. The process of claim 39 wherein R_3, R_4 and R_5 are H and R_2 is selected from the group consisting of phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, naphthyl, quinolyl, and $(CH_2)_{1-6}$ cycloalkyl (C_3-C_8).

43. The process of claim 39 wherein X_4 is selected from the group consisting of CN, NO_2, $CONH_2$, CHO, CO_2CH_3, and $CO_2C_2H_5$.

44. The process of claim 39 wherein R_2 is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl.

45. The process of claim 39 wherein R_1 is an optionally substituted pyridyl.

46. The process of claim 39 wherein R_1 is an optionally substituted pyrimidyl.

47. The process of claim 39 wherein step (a) is carried out in the presence of a base.

48. The process of claim 39 wherein step (a) is carried out in the presence of a solvent.

49. The process of claim 48 wherein said solvent is acetonitrile.

50. The process of claim 48 wherein said solvent is a mixture of acetonitrile and water.

51. A sweet foodstuff including one or more compounds of Claim 1 as the sweetening agent.

52. An edible composition comprising

(a) a foodstuff; and

(b) one or more sweetening agents selected from the group consisting of the compounds of Claim 1.

53. A process comprising

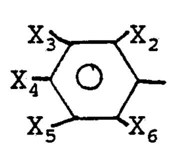
(a) reacting a compound of the formula

$$R_1NH_2$$

with a compound of the formula

$$X_1CN - \overset{R_2\ \ R_3}{C} - \underset{R_4\ \ R_5}{C} - COOR_6$$

wherein X_1 is O or S, wherein R_1 is an optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, said phenyl corresponding to:



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are

selected from the group consisting of:

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
$CH=NOCH_3$,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
$CH=NOH$,
CHO,
CH_2OCH_3,
CH_2OH,
CN,
$COCF_3$,
COC_1-C_3 alkyl,
$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,
$COOC_1$-C_3 alkyl,
COOH,
NH_2,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
NHCHO,
$NHCOCH_3$,
$NHCONH_2$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 may not be OCH_2CH_3
$OCOCH_3$,
OH,

SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2N(C_1$-C_3 alkyl$)_2$,
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring,

wherein R_2, R_3, R_4, and R_5 are the same or different and are selected from the group consisting of
H,
optionally substituted straight chain or branched C_1-C_{10} alkyl,
optionally substituted cyclic C_3-C_{10} alkyl, optionally substituted cyclic,
optionally substituted heterocyclic including optionally substituted heteroaromatics, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, and enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining groups is not H; and

and wherein R_6 is methyl, ethyl, propyl, or butyl, and

(b) hydrolyzing the resulting compound; and

(c) recovering the isolated desired urea compound or salt thereof formed in step (a).

54. The edible composition of claim 53 further comprising a sweetening agent selected from the group consisting of

sucrose, corn syrups, fructose, aspartame, alitame, neohesperidin dihydrochalcone, high fructose corn syrup, hydrogenated isomaltulose, stevioside type sweeteners, L-sugars, lactitol, neosugar glycyrrhizin, xylitol, acesulfam-K, sodium saccharin, potassium saccharin, calcium saccharin, cyclamic acid and the sodium, potassium, and calcium salts thereof, sucralose, monellin, thaumatin and mixtures thereof.

55. The edible composition of claim 53 comprising a beverage.

56. The edible composition of claim 53 comprising a confection.

57. A composition for use in preparing the compositions of claim 1 corresponding to the formula

$$H_2N-C(R_2)(R_3)-C(R_4)(R_5)-COOH$$ or salts thereof

wherein R_2, R_3, R_4, and R_5 are the same or different and are selected from the group consisting of

H,

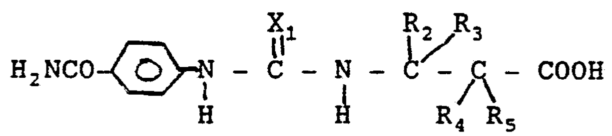
optionally substituted cyclic C_3-C_{10} alkyl,

optionally substituted straight chain or branched C_1-C_{10} alkyl

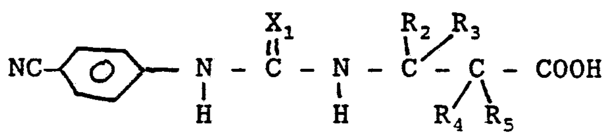
optionally substituted cyclic,

optionally substituted heterocyclic including substituted heteroaromatics, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, and enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2, at least one of the group R_2, R_3, R_4, and R_5 is not H and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining groups is not H.

58. A process for producing a first urea or thiourea of the formula

 and all salts thereof

from a second urea or thiourea of the formula

 and all salts thereof

wherein X_1 is O or S, and wherein

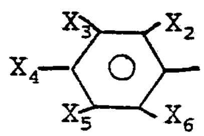
R_2, R_3, R_4 and R_5 are the same or different and are selected from the group consisting of:
H
optionally substituted straight chain or branched C_1-C_{10} alkyl,
optionally substituted cyclic C_3-C_{10} alkyl,
optionally substituted cyclic,
optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl,
and enantiomers and physiologically acceptable salts thereof, said process comprising the step of:
reacting said second urea or thiourea with alkaline hydrogen peroxide to produce said first urea or thiourea.

59. A process for obtaining one isomer of a first compound of the formula:

$$R_1 - \underset{H}{N} - \overset{X_1}{\overset{\|}{C}} - \underset{H}{N} - C(R_2)(R_3) - C(R_4)(R_5) - COOH$$ and all salts thereof

wherein X_1 is O or S, R_1 is

an optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, said phenyl corresponding to:



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are selected from the group consisting of

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
$CH{=}NOCH_3$,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
$CH{=}NOCH_3$,
CH=NOH,
CHO,
CH_2OCH_3,
CH_2OH,
CN,
$COCF_3$,
COC_1-C_3 alkyl,
$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,

$COOC_1$-C_3 alkyl,
COOH,
NH_2,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
NHCHO,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
$NHCOCH_3$,
$NHCONH_2$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 may not be OCH_2CH_3
$OCOCH_3$,
OH,
SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2N(C_1$-C_3 alkyl$)_2$
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring,

R_2 and R_3 are the same or different and are selected from the group consisting of

H,
optionally substituted straight chain or branched C_1-C_{10} alkyl,

optionally substituted cyclic C_3-C_{10} alkyl, optionally substituted cyclic, optionally substituted heterocyclic, optionally substituted bicyclic, or optionally substituted phenyl, and enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining group is not H,

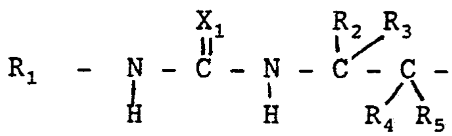
comprising the steps of:

reacting an aldehyde with an amine to produce a Schiff base;
reacting said Schiff base with a methyl haloacetate and a metal to produce a diastereomeric mixture of a β-lactam;
hydrolyzing said β-lactam to produce a diastereomeric mixture of a first β-amino acid;
esterifying said first β-amino acid;
isolating one isomer of the ester of said diastereomeric mixture of said first β-amino acid;
hydrogenolyzing said ester to produce one stereoisomer of a second β-amino acid;
reacting said stereoisomer of the second amino acid with an isocyanate or isothiocyanate to produce said first compound.

60. The process of claim 59 wherein said metal is zinc.

61. The process of claim 59 wherein said second β-amino acid is produced by reaction of said first β-amino acid with palladium and carbon.

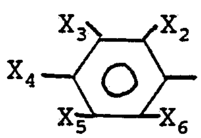
62. A process for obtaining one isomer of a first compound of the formula:



and all salts thereof

wherein X_1 is O or S, R_1 is

an optionally substituted cyclic, optionally substituted heterocyclic including optionally substituted heteroaromatic, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, said phenyl corresponding to:



wherein X_2, X_3, X_4, X_5 and X_6 are the same or different and are selected from the group consisting of

H,
CF_3,
CF_2CF_3,
CH_2CF_3,
C_1-C_4 alkyl,
CH=NOCH3,
$CH=NOCH_3$,
Cl, with the proviso that X_3 and X_5 may not both be Cl,
Br,
I,
F,
CH=NOH,
CHO,
CH_2OCH_3,
CH_2OH,
CN,

$COCF_3$,
COC_1-C_3 alkyl,
$CONH_2$,
$CONHC_1$-C_3 alkyl,
$CON(C_1$-C_3 alkyl$)_2$,
$COOC_1$-C_3 alkyl,
COOH,
NH_2,
NHC_1-C_3 alkyl,
$N(C_1$-C_3 alkyl$)_2$,
NHCHO,
$NHCOCH_3$,
$NHCONH_2$,
$NHSO_2CH_3$,
C_1-C_3 alkyl COOH,
NO_2,
OC_1-C_3 alkyl, with the proviso that X_4 may not be OCH_2CH_3
$OCOCH_3$,
OH,
SC_1-C_3 alkyl,
SOC_1-C_3 alkyl,
SO_2C_1-C_3 alkyl,
SO_2NH_2,
SO_2NHC_1-C_3 alkyl,
$SO_2N(C_1$-C_3 alkyl$)_2$,
SO_3H,
and where substituents at any two of X_2, X_3, X_4, X_5 or X_6 form a fused ring,

R_2 and R_3 are the same or different and are selected from the group consisting of

H,
optionally substituted straight chain or branched C_1-C_{10} alkyl,

optionally substituted cyclic C_3-C_{10} alkyl, optionally substituted cyclic, optionally substituted heterocyclic including heteroaromatics, optionally substituted bicyclic including optionally substituted aromatic bicyclic, or optionally substituted phenyl, and enantiomers and physiologically acceptable salts thereof with the proviso that if X_4 is NO_2 or CN, at least one of the group R_2, R_3, R_4, and R_5 is not H, and if one of the group R_2, R_3, R_4 and R_5 is CH_3, at least one of the remaining group is not H,

comprising the steps of:

reacting an aldehyde with an amine to produce a Schiff base;
reacting said Schiff base with methyl haloacetate and a metal to produce a diastereomeric mixture of a β-lactam;
isolating one diastereomer of said β-lactam;
hydrolyzing said isomer of said β-lactam to produce one stereoisomer of first β-amino acid;
hydrogenolyzing said stereoisomer of first β-amino acid to produce one stereoisomer of said second β-amino acid;
reacting said stereoisomer of said second β-amino acid with an isocyanate or isothiocyanate to produce said first compound.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US89/03616

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC
IPC(4): C07C 127/19; A23L 1/236
U.S.Cl.: 558/413,414,415,416,417; 560/251; 562/426,428,430,439

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	558/413,414,415,416,417; 560/251; 562/426,428,430,439

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Chemical Abstract Structure Search (Online)
1966 - To Date

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Chemical Abstracts, Vol. 94, No. 23 Abstract 186 226x issued 8 June 1981, (Columbus, Ohio, U.S.A.) Tinti et al. "Studies on sweeteners requiring the simultaneous presence of both nitrogen dioxide/cyanide and carboxyl groups".	1(part)-38,51&52
A	Chemical Abstracts, Vol 106, No. 25, Abstract 214 377j issued 22 June 1987 (Columbus, Ohio, U.S.A.) Tsuchiya et al "Amino acid derivatives as sweeteners".	1(part)-38, 51&52
X	The Merck Index. Tenth Edition published by Merck and Co, Inc. Rahway, N.J. (1983) page 1293, entry no. 8886.	1(part)-3 6-13,17 20.21. 30-38 51 and 52

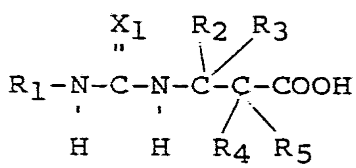
* Special categories of cited documents: [10]
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 OCTOBER 1989	15 DEC 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	ZINNA NORTHINGTON-DAVIS

PCT/US89/03616
Attachment sheet 1

GROUP I: Claims 1(part)-38, 51 and 52, drawn to the formula



wherein R_1 represents cyclic heterocyclic, heteroaromatic, bicyclic, aromatic bicyclic and phenyl.

GROUP II: Claims 39 50, drawn to a process of preparing compounds of GROUP I.

GROUP III: Claims 53-56. drawn to a process of preparing compounds of GROUP I.

GROUP IV: Claim 57 drawn to a process of preparing compounds of GROUP I.

GROUP V: Claim 58 drawn to a process of preparing urea or thiourea compounds of GROUP I.

GROUP VI: Claims 59-61 drawn to a process of preparing an isomeric compound of GROUP I.

GROUP VII: Claim 62 drawn to a process of preparing an isomeric compound of GROUP I.

PCT/US89/03616

Detailed Reasons for Holding Lack of Unity of Invention

There is a lack of a significant common structural moiety in GROUP I wherein R^1 represents cyclic, heterocyclic, heteroaromatic, bicyclic, aromatic bicyclic and phenyl to which the claimed utility (sweetening agent) may be attributed.

Inventions I and (II to VII) are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process. In the instant case the product as claimed can be made by a materially different process such as GROUPS II to VII.

Accordingly, the requirement of the unity of invention have been set forth which includes a single general inventive concept.